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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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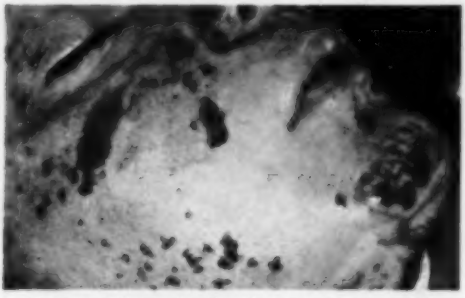

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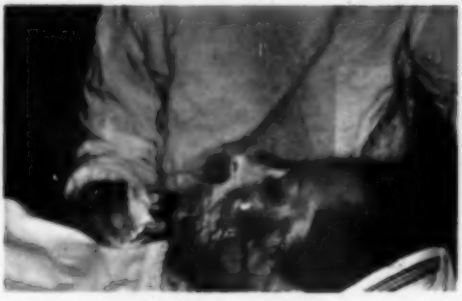

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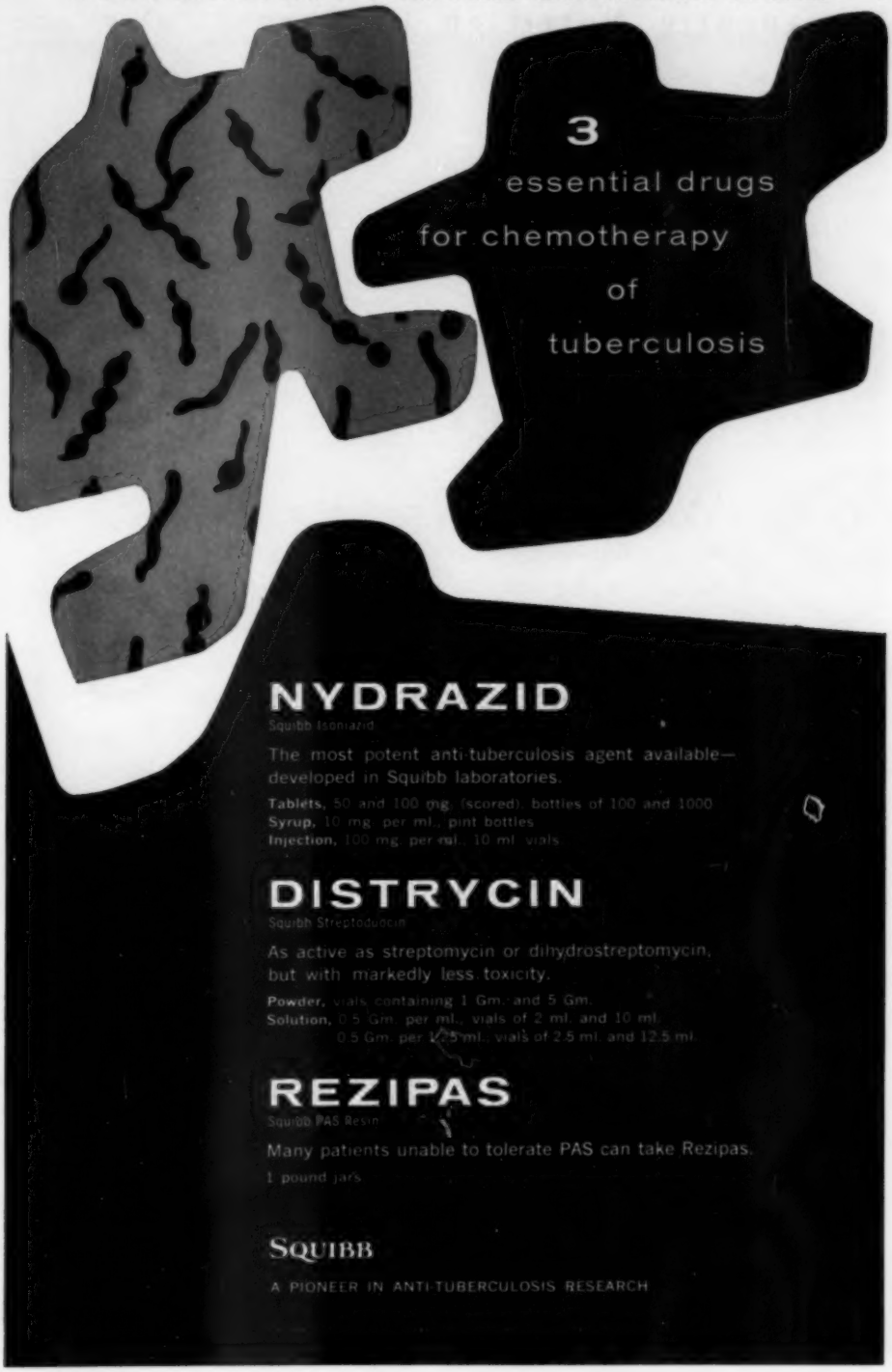
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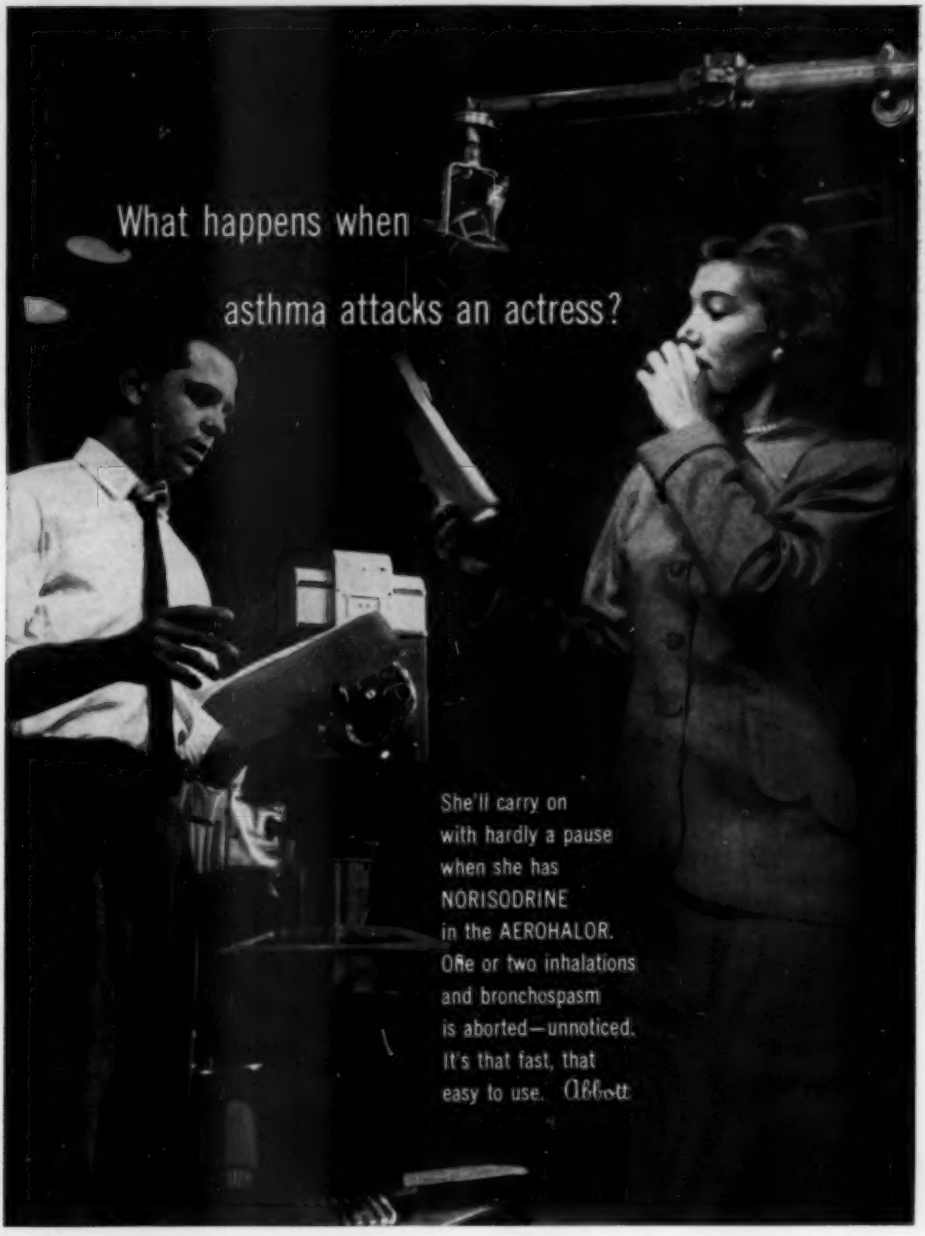

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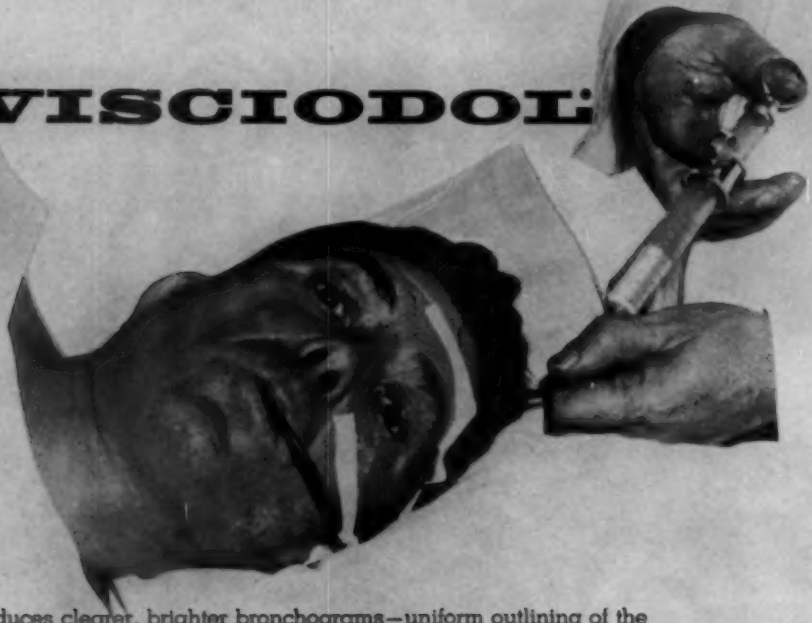

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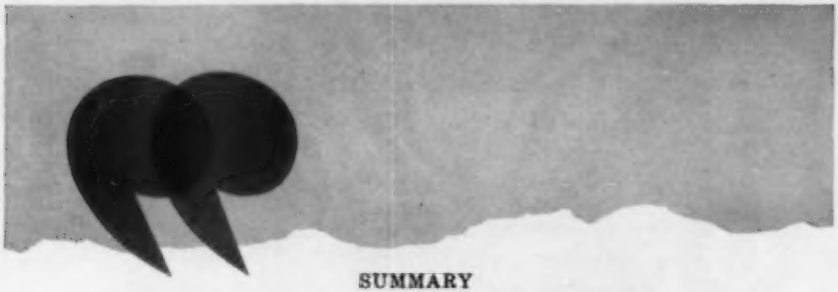

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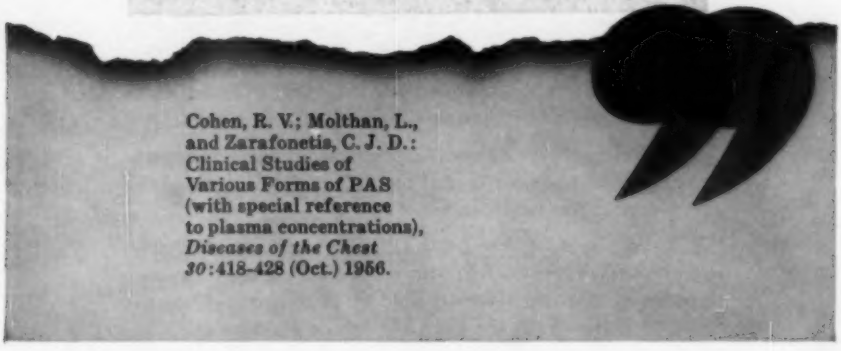

Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

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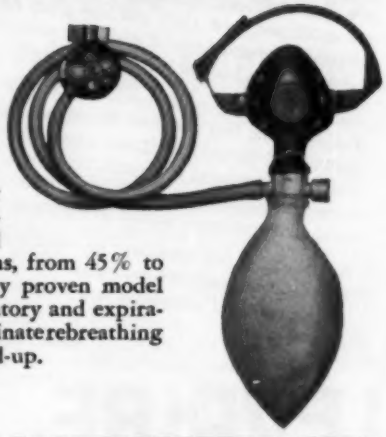

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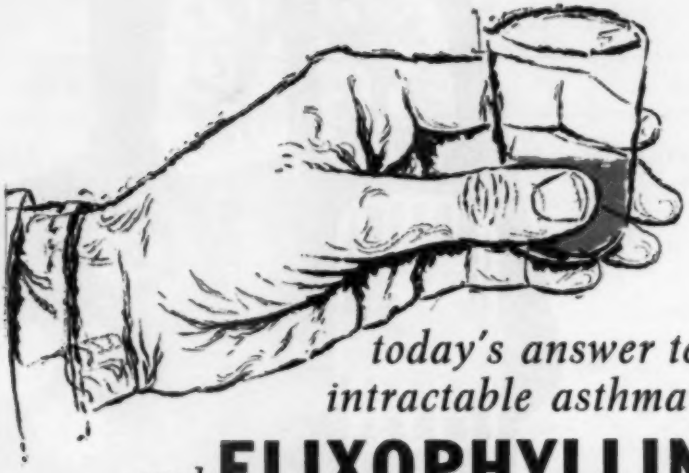

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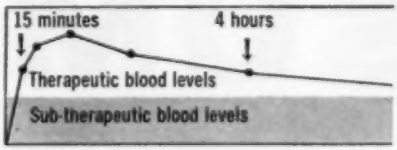

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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

VOLUME 77 *February, 1958* NUMBER 2

THE CHEST ROENTGENOGRAM AND CHEST ROENTGENOGRAPHIC SURVEYS RELATED TO X-RAY RADIATION EFFECTS AND PROTECTION FROM RADIATION EXPOSURE[1]

Executive Committee of the American Trudeau Society

(Received for publication October 15, 1957)

The roentgenographic examination of the lungs has been one of the most important and dependable tools of the thoracic physician and surgeon and public health worker in early diagnosis and treatment of unsuspected chest disease. The chest roentgenogram continues to be an important part of all tuberculosis case-finding programs. The National Tuberculosis Association in 1955 summarized the modern usefulness of the technique of chest roentgenographic surveys with far reaching principles concerning its application.[2] The following are a few of the recommendations it stressed:

> Tuberculosis, lung cancer, nontuberculous pulmonary infections, intrathoracic tumors, and cardiovascular abnormalities are conditions for which lasting cure depends upon early diagnosis of the often unsuspected lesion by chest X-ray techniques.
>
> Immediate follow-up and proper handling of every thoracic abnormality is necessary.
>
> The general hospital roentgenographic admission program as a survey technique is most productive in turning up previously unsuspected thoracic disease.
>
> The relative costs of the various types of X-ray machines were presented and found dependent on the number of films taken. This information is a contribution from the United States Public Health Service.

In June, 1956, the National Academy of Sciences, National Research Council, called attention to the effects of X-ray radiation, particularly resulting from atomic bomb explosions. Their studies covered the "Biological Effects of Atomic Radiation" especially as it affects the human body and its reproductive organs. Later reports discussed the possibilities of effects of body radiation upon the

[1] This report by the Executive Committee of the American Trudeau Society on X-ray radiation effects and protection from radiation exposure is the result of a conference with expert advice, held in Chicago on October 8, 1957, at the Del Prado Hotel.

[2] Chest X-Ray Screening Programs in General Hospitals, National Tuberculosis Association, 1955.

blood system, with leukemia as a delayed effect. All of these subjects remain controversial, but this discussion on radiation effects has led everyone—scientist, physician, and layman—to think deeply concerning them and to evaluate programs of action based thereon.

The problem is therefore one of weighing the benefits from roentgenographic diagnostic procedures against the liability of harmful effects of radiation exposure.

There are few good human data on this aspect of low doses of ionizing radiation and most of the factual information has come from animal experimentation. Nonetheless, the unknown as well as the known effects of radiation exposure impose a definite responsibility to the public.

In people who are ill, the needs for roentgenographic studies are great and deserve more weight on the side of diagnostic benefits as opposed to possible hazardous effects of radiation. In any case, all radiation exposure that serves no useful purpose should be scrupulously avoided.

It is well recognized concerning X-ray machines that there is no standard pattern of radiation exposure delivered by any standard type of unit. It has been shown that each X-ray unit, photofluorographic or conventional, delivers its own peculiar amount and type of X-ray radiation. Therefore each machine must be tested individually and carefully for its own output of radiation and must be provided with all necessary safety devices for minimizing gonadal and general body radiation. This must be done by persons trained in radiologic protection.

Proper Indications for Chest Roentgenograms

The American Trudeau Society has taken leadership in emphasizing that there is no virtue in the taking of chest roentgenograms per se. Roentgenograms are only justified if they lead to the detection of previously unsuspected or clinically significant, curable lung disease, followed by appropriate therapy. If the abnormalities disclosed are not followed up, radiation has been wasted.

Therefore, it is essential for those engaged in the detection of pulmonary disease to evaluate their yields on a continuing basis. These yields vary from one community to another and from time to time but, in general, are higher among certain population segments. Among these high-yield groups, periodic chest roentgenograms are the most practicable approach. Among infants, children, young adults, prenatal patients, and especially young diabetics, the tuberculin test should be used as the preliminary screening technique whenever possible, and the tuberculin reactors should have roentgenographic examinations of the lungs for the detection of tuberculosis. The nonreactors among these groups should be rechecked periodically by means of the tuberculin test. However, aside from screening considerations, every child should have a single roentgenogram for the identification of congenital or developmental defects and nontuberculous disease and for comparison with any films taken later in life. In the younger age groups particularly, only those X-ray units that meet modern requirements for radiation protection should be used.

Choice of Appropriate X-ray Apparatus

Three types of equipment are in general use for chest roentgenographic survey purposes. Other factors being equal, the amount of radiation necessary for a satisfactory chest film is least with a standard 14- by 17-inch film in a cassette with intensifying screens. Compared with the standard 14- by 17-inch X-ray unit, there is approximately three to five times more radiation using the mirror optics photofluoroscopic unit and about ten to twenty times the radiation exposure when using the standard lens camera photofluorographic machine. This in well-protected X-ray units is still a very small amount of radiation, but these figures may be multiplied by 100 if the apparatus is not properly equipped with protective devices. The difference in radiation exposure between the standard 14- by 17-inch and other photofluorographic X-ray units is less than the difference between a well protected and a poorly protected machine.

For practical purposes, these differences in radiation requirements appear to be of less relative importance at this time than the proper operation of equipment with adequate protective devices. When the number of survey films taken per day is small or when modern protective devices have not been installed, it is better to use standard 14- by 17-inch films, even though the cost per film is higher than for a photofluorographic unit.

When the number of films taken per day is large, or the machine must be moved frequently as in a mobile unit, a properly equipped photofluorographic unit is the most practical apparatus. The increased amount of radiation involved in such photofluorographic units is small and is warranted in those segments of the population where the yield of new cases is significant.

Whenever the purchase of a new photofluorographic unit is contemplated, the mirror optical system camera is to be preferred over the ordinary lens system. The reduction in radiation with this device and the superiority of results will justify a substantial difference in price

Screening of groups by fluoroscopy should be strongly discouraged for several reasons: the results are not accurate for diagnostic purposes; there is no permanent film record of the examination; and the radiation exposure involved both for the subject and the examiner is excessive. However, special fluoroscopic examination may be indicated for specific diagnostic purposes and for the determination of the dynamics of the chest.

Laminagrams, even with properly operated equipment, can result in a substantial radiation exposure to the chest, and should be used only for special diagnostic problems.

The Nature of Radiation Effects

Populations are being exposed to a variety of radiations from natural and artificial backgrounds as well as from medical diagnostic and therapeutic procedures. The average exposure received by the population today from all sources appears to be at a lower level than that which has been demonstrated to produce harmful effects in humans and experimental animals.

At this time the effects of small doses of radiation are unknown. Speculation

is based on statistical calculations projected downward from the known effects of higher doses used in experimental animals and derived from atomic explosions. These effects from higher doses may manifest themselves as genetic changes resulting from radiation of the gonads, or general body effects with leukemia or other delayed pathologic changes as rare sequelae. It should be emphasized that unnecessary radiation should always be avoided by conducting medically supervised programs with properly operated equipment and adequate follow-up plans.

Techniques for Minimizing Exposure

Those responsible for screening programs should ensure that steps have been taken to maintain the radiation dose at the lowest practicable level both to those being examined and to equipment operators. Techniques are available to accomplish this at nominal cost, and should be applied wherever not already in use. These techniques include:

1. *Proper coning:* This is particularly important in reducing the gonadal dosage. Cones should be rectangular in shape and should limit the primary beam to an area no larger than that visualized on the film. Adequate cones should be continuously mounted on all units. Misalignment of the cone results in "cone cutting" of film. Technicians often remove cones or use too large an aperture to avoid "cutting" the film. This should never be permitted. Precise and accurate alignment, rather than removal of the cone, is the proper remedial procedure in this case. Mechanical linkage of the tube and film holder or the use of light localizers are useful when feasible.

2. *Proper filtration:* This should be assured by permanently mounting at least 2 millimeters of aluminum filtration, or its equivalent, in the primary beam. When technical factors permit, filtration up to 3 millimeters should be used, and this is better than 2 or 2.5 millimeters.

3. *Shielding:* Proper shielding of both the direct beam and the scatter radiation should be provided. Its adequacy for protection of equipment operators, their assisting personnel, waiting patients, and the general public should be assured by adequate radiation surveys.

4. *Adequacy of tube housing:* This is a protective barrier and should be checked by a radiation survey. In addition to its over-all effectiveness, special attention should be paid to the possibility of small defects which will result in leakage of direct radiation in directions other than that of the useful beam.

5. *Technical factors:* Significant reductions in patient and operator dosage can often be obtained by use of higher kilovoltage techniques. Optimal operating voltage will vary with equipment. Higher speed screens and films should also be employed.

6. *Tube-to-skin distance:* This should be kept as high as possible. Five- or six-foot distances are advisable.

7. *Exposure control:* These should be so arranged that operation of the equipment is impossible except with the operator behind a suitable protective barrier.

In addition, more advanced and expensive technical improvements can result in a reduction of patient and operator dosage. Examples of these improvements

are mirror optics and electronic image amplification. Widespread applications of such techniques can be deferred, however, pending a concerted effort to accomplish the modifications noted above, when needed. Early implementation of recommendations regarding coning and filtration should be undertaken without awaiting availability of complete radiation surveys.

Where not already accomplished, suitable instruction of personnel in optimal operating and film-processing techniques should help keep diagnostic value high and minimize the necessity for re-examinations.

The principles outlined above are equally applicable in individual diagnostic studies. When fluoroscopy is involved, additional emphasis should also be placed on minimal field size, adequate adaptation to darkness, and tube-to-table-top distance which should be at least 18 inches.

Conclusions

The kernel of the problem of radiation effects is the awareness by the public, physicians, and tuberculosis workers that the whole subject is one of weighing the benefits of radiography against the effects of radiation exposure. It should remain clear that radiation that serves a useful and necessary purpose is warranted, but it should be used with the best protective devices to minimize exposure. Putting the chest roentgenographic examination in its proper perspective, the radiation exposure to the gonads or body from a single chest film, using a well-monitored machine, is infinitesimal when compared to the commonly used roentgenographic diagnostic procedures directly involving the gonadal areas.

Recommendations

Several specific recommendations from this report can be made to the medical, professional, and interested groups, such as the constituent associations of the National Tuberculosis Association and the American and state Trudeau societies.

1. Chest roentgenographic surveys must be continued not only in the field of tuberculosis, but in the detection of cancer, industrial thoracic disease, acute and chronic nontuberculous infections, chest tumors, and cardiovascular abnormalities.

2. Conventional and photofluorographic X-ray units may be used to survey segments of the population which are expected to show a high yield of thoracic disease, but the X-ray machines must be equipped with adequate protective devices.

a. The purchase of certain protective devices should be made *now* without waiting for the more complete monitoring of the unit. These include proper cones, proper filtering, shielding devices for subject and operator, and exposure controls of automatic nature.

3. Tuberculin testing in infants, children, young adults, prenatals and young diabetics should be developed as a primary guide to tuberculosis contacts and as one case-finding method. A roentgenogram of the chest for the detection of tuberculosis could then be limited to those with positive tuberculin tests.

4. Reassessment of case-finding programs should be done concerning

those segments of the population most deserving of chest roentgenographic surveys or tuberculin testing.

5. The instruction and training of personnel should include information concerning the protective devices for all types of X-ray units.

6. Education of health workers and the public should be undertaken with a positive program incorporating this new and more optimistic look concerning chest roentgenographic examination. It should be made known to all concerned that effective steps have been taken to minimize direct and scatter radiation exposure involved in taking chest roentgenograms. A constructive approach is in order to emphasize the continuing usefulness and the need for early diagnosis and treatment of all forms of pulmonary disease.

7. Members of the American Trudeau Society and constituent associations of the National Tuberculosis Association might well assume an active role in assisting in and promoting the training of personnel skilled in radiation protection. Such a program could develop and assume a most important role in assuring the confidence of the public that the leadership of these organizations in the field of thoracic disease carries with it the certainty of minimal radiation exposure and the maximal protection whenever chest roentgenographic examinations are used in survey and diagnostic work under their sponsorship.

The members of the Committee and others who attended the conference are listed below.

Expert Technical Advisors

Richard H. Chamberlain, M.D.
Professor of Radiology
University of Pennsylvania
School of Medicine

Clinton Powell, M.D.
Chief, Radiological Health Medical Program,
U. S. Public Health Service

Asher J. Finkel, M.D.
Health Director
Argonne National Laboratories
Lemont, Illinois

National Tuberculosis Association Staff Members

Floyd M. Feldmann, M.D.
Medical Director
National Tuberculosis Association

James E. Perkins, M.D.
Managing Director
National Tuberculosis Association

Frank W. Webster
Executive Secretary
American Trudeau Society

Executive Committee, American Trudeau Society

Katharine R. Boucot, M.D.
Ejvind P. K. Fenger, M.D.
Daniel E. Jenkins, M.D.
Roger S. Mitchell, M.D.
Paul C. Samson, M.D.
Joseph B. Stocklen, M.D.
Theodore L. Badger, M.D., *Chairman*

RESPIRATORY FUNCTION FOLLOWING SEGMENTAL RESECTION OF THE LUNG FOR BRONCHIECTASIS[1]

ROBERT KAMENER, MARGARET R. BECKLAKE,[2] HYMIE GOLDMAN, AND MAURICE McGREGOR

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INTRODUCTION

Although lung disease has been treated by surgical resection for many years, considerable uncertainty prevails as to the physiologic status of the remaining lung following operation. Ideally, surgery should aim at the removal of functionless tissue only, leaving the rest of the organ intact. In the case of the lung, this ideal may be difficult to realize as the removal of lung tissue may affect the mechanics of the remaining healthy lung as well as the cardiovascular system.

Experimental studies on the consequences of pneumonectomy in the dog by Longacre and Johansmann (1) suggest that the changes in the remaining lung vary according to the age of the dog at the time of operation. Following the operative removal of one lung in the immature puppy, a considerable amount of hyperplasia of remaining lung tissue occurred and the general condition remained excellent. On the other hand, a dog operated on after maturity showed great deviations from the normal, such as a drop in arterial oxygen saturation, an irregular pulse, and gross elevation of body temperature on exercise. Another significant difference in the behavior of the adult dog was that his condition deteriorated with the lapse of time. Histologically, there was destruction of alveolar walls, collapse of capillaries, and decreasing lung elasticity.

Rienhoff, Reichert, and Heuer (2), studying changes in the cat lung, found that surgery merely produced a dilatation of the lung units. There was no evidence of alveolar or elastic tissue destruction. Their study, however, was confined to a six-month postoperative period, which may have been inadequate for the development of the changes described by Longacre and Johansmann.

Cournand, Himmelstein, Riley, and Lester (3) have made long-term studies on four young patients on whom pneumonectomies had been performed for suppurative disease. Two of these patients did not subsequently become hyperinflated, in so far as following surgery their residual volumes never exceeded the predicted value for one lung. In these two cases values for maximal breathing capacity were within the low normal range and arterial oxygen saturation was normal at rest and on extreme effort. In the other two cases, however, postoperative values for residual volume were more than those predicted for the remaining lung alone. Moreover, in these two cases maximal breathing capacity

[1] From the Cardiopulmonary Unit of the Council for Scientific and Industrial Research and the Department of Medicine of the Witwatersrand University Medical School, and the Johannesburg Hospital, Johannesburg, South Africa.

[2] In receipt of a bursary from the Pneumoconiosis Research Unit of the Council for Scientific and Industrial Research.

was low and a fall of arterial oxygen on strenuous effort was observed. This suggested that, in the young individual as well as in the puppy, function remains good if there is no overdistension. In a subsequent study, Cournand, Riley, Himmelstein, and Austrian (4) again reached the conclusion that overdistension when it occurred caused the lung function to deteriorate, even to a degree which might justify thoracoplasty as a corrective procedure.

The effect of surgical removal of various amounts of lung on the function of the remaining lung has been the subject of several other studies, the results of which have not always been in agreement. While some investigators have found a pattern consistent with developing emphysema in the remaining lung (5), others have reported overdistension alone without any other evidence of disturbances of function (6). In some instances conclusions have been based on postoperative studies only, a procedure which may be misleading in a condition such as bronchiectasis in which diffuse lung disease may exist.

Thus, it is uncertain whether loss of lung tissue may be expected simply to subtract from the pulmonary reserve in proportion to the volume of tissue lost or whether the remaining lung itself may be expected to deteriorate in function and, in the case of surgical resection for bronchiectasis, whether an over-all deterioration of function is to be anticipated.

With the intention of throwing some light on this problem, a review has been made of the pulmonary function of a series of bronchiectatic subjects before and at various intervals following segmental resection.

Material and Methods

Twenty-one cases were studied, 5 males and 16 females, ranging in age from fourteen to forty-eight years (table 1). Most were patients in whom bilateral operation was contemplated, and therefore were cases of more than average severity. The patients were not preselected in any other way. The number of pulmonary segments removed varied from 3 to 10. In 16 cases a single operation only was involved; in 5 cases bilateral resection was performed. Wherever possible, the subjects were tested immediately before operation, at a short time (one to four months) postoperatively, and a year or more thereafter. Cough and sputum were the principal complaints of all patients (table 1). Neither congestive heart failure nor roentgenographic evidence of cor pulmonale was observed in any case.

Spirometry was performed on all subjects to measure vital capacity and maximal breathing capacity. Functional residual capacity was measured by the closed-circuit constant-volume method of McMichael (7) with certain adaptations (8). From the rate at which the lungs equilibrated with this circuit, a mixing index was calculated (9, 10).

An exercise test of the type described by Hugh-Jones (11) was done by each subject (load 300 kg.m. per minute for five minutes) and the arterial oxygen saturation at rest, during this exercise, and after breathing pure oxygen was recorded by oximetry.[3] When necessary all values were adjusted to make the oximetric reading on oxygen equal 100 per cent.

In the cases tested during 1955 and subsequently, the mechanics of breathing were studied by comparing intra-esophageal pressure with the rate of air flow. Intra-esophageal pressure was measured using a tube of the type described by Mead and Whittenberger (12) and a straingauge manometer,[4] while air flow was measured by means of a Lilly pneumotachograph screen. In the earlier cases, tidal volume was calculated by integration of the pneumotachograph tracing. More recently, volume was derived by Boyle's law from the pressure changes recorded in a large box into which the patient breathed (13). Com-

[3] Waters Conley Absolute Reading Oximeter.

[4] Statham Straingauge P23A and P6.

TABLE 1

SUMMARY OF CLINICAL DATA ON THE 21 CASES OF BRONCHIECTASIS STUDIED

Case Number*	Sex	Age at Time of Operation	Duration of Symptoms	Dyspnea		Cough		Sputum		Improvement in General Health After Operation	Number of Segments in Which Lesions Are Present	Time(s) of Study (months postoperatively)
				Preoperatively	Postoperatively	Preoperatively	Postoperatively	Preoperatively	Postoperatively			
		years	*years*									
3A	F	40	16	2		+++	++	+++	++	Marked	4	5
3B	F	22	18	0–1	2	++	++		+	Slight	?	7, 18
4A	M	30	3		0	++	+	++	+	Moderate	4	1, 53
4B	F	35	34	2	1	+++	+	++	+	Marked	1	3
4C	F	29	29	0	0	++	+	++	0	Moderate	5	5
4D	M	33	12	0–1	0–1	++	++	++	++	None	5	5
4E	F	34	30	1	1	++	+	+++	++	None	0	2
5A	M	30	30	2	2	+++	++	++	++	None	0	9
5B	M	27	27	1	1	+++	+	+++	+	Slight	5	6
5C	F	20	19	0		++		+++		Moderate	0	1
5D	F	20	20	2	2–3	++	+	+++	++	Slight	5	7
5E	F	20	17	2	1–2	+++	+	+++	+	Moderate	5	6
5F	F	21	20	0–1	0	+++	+	++	+	Marked	5	3, 12
6A	F	14	14	1	1–2	+++	++	++	++	None	0	2, 7, 50
6B	F	20				+++	++	++	+		2	4, 11
6C	F	22		0	0–1	++	+	++	+	Moderate	2	2, 10, 16, 60
6D	M	48	47	0	0	++	+	+++	++	Moderate	5	11, 21
7A	F	26	25	0	0–1	+++	++	++	+	None	5	4
8A	F	28	28	1	0	++	+	+++	+	Marked	?	4, 8, 12
10A	F	16	16	1	0	++	0	+	0	Marked	0	3, 6, 12, 48
10B	F	25	21	1	1–2	+++	++	++	+	Slight	0	9, 17, 50

* The number of the patient reveals the number of segments of lung finally resected

pliance (expressed as Ls. per cm. of water pressure) was estimated by relating tidal volume to the intrathoracic pressure difference at end-inspiration and end-expiration. Resistance (expressed as cm. per L. per sec.) was calculated at the points during inspiration and expiration at which the pressure required to cover nonelastic resistance was maximal.

Certain results were compared with the predicted normal value for the particular individual, namely, vital capacity, residual volume, functional residual capacity, and maximal breathing capacity (14). The prediction formulas used were based on a study of 94 normal subjects of various ages, resident at this altitude (5,670 feet above sea level) in which test results were correlated with four body characteristics, namely, age, height, weight, and surface area; and prediction formulas based on one or more of these variables were derived by the standard statistical techniques of partial correlation. The predicted values used for comparison were those for both lungs, no allowance being made for the tissue removed at operation.

The influence of resection on pulmonary vascular function was not investigated.

RESULTS

Most patients reported an improvement in general health following surgery (table 1). Sputum, cough, and frequent bronchopulmonary infections notably

decreased following operation. Six patients believed that they now became breathless more easily, although the deterioration appeared very slight and was difficult to assess objectively. The majority felt unchanged or a little better in this respect. Two subjects (*Cases 8A* and *10A*) thought that the improvement postoperatively had been considerable. This was to some extent borne out by the response to the exercise test.

Changes in lung function tests are reflected in tables 2, 3, and 4. Prior to operation the mean *functional residual capacity* of the whole group was greater than normal, being 110 per cent of the predicted value (table 2). Immediately after operation there was a fairly substantial reduction in functional residual capacity, which was not, on the whole, proportional to the extent of the resection (mean functional residual capacity of the 9 patients measured within four months of surgery was 87 per cent). When measured later than this, however, there was a general tendency for the values to increase, and the mean value in 17 patients examined more than four months postoperatively was 110 per cent. Furthermore, the ultimate value for functional residual capacity appeared related to the age of the patient at the time of operation. The 6 patients who were twenty years of age and less had a mean preoperative functional residual capacity of 111 per cent. This figure dropped postoperatively and did not exceed 99 per cent even at the latest postoperative examinations. For patients between the ages of twenty-five and thirty years, however, the mean preoperative functional residual capacity value of 111 per cent was exactly equaled at the final postoperative examination. There were 3 patients in the series who were older than thirty. In these the mean functional residual capacity value rose from a preoperative figure of 117 per cent to 126 per cent of the predicted value at the final postoperative test.

Residual volume approximately paralleled the values for functional residual capacity. Prior to operation it tended to be elevated. Surgery was followed by a sharp decrease during the immediate postoperative period, but with the lapse of time the preoperative level was again approximated.

Preoperatively, the *vital capacity* was abnormally low in 17 subjects. Immediately after operation there was a further reduction in most cases. With the passage of time, however, there was a marked tendency for vital capacity values to return to—and in some instances exceed—the preoperative figures. The data

TABLE 2

MEAN VALUES FOR LUNG VOLUMES MEASURED PREOPERATIVELY, WITHIN FOUR MONTHS OF OPERATION, AND LATER

Months Postoperatively	Vital Capacity		Residual Volume		Functional Residual Capacity	
	Per Cent Predicted	Number of Cases	Per Cent Predicted	Number of Cases	Per Cent Predicted	Number of Cases
Preoperatively..	77	(21)	147	(20)	110	(20)
0–4.....	58	(10)	115	(9)	87	(9)
>4.....	71	(17)	135	(17)	110	(17)

TABLE 3

WORK OF BREATHING STUDIES IN 12 SUBJECTS WITH BRONCHIECTASIS

Subject	Months Postoperatively	Resistance cm/L/sec.		Compliance at Rest	Rate	Compliance on Hyperventilation	Rate	Resting End Expiration Level
		Inspiration	Expiration					
				L/cm.		*L/cm.*		*cm. H_2O*
Mean Value*		1.86	2.04	0.219	20			
3A	Preoperatively	5.50	6.69	0.174	16	0.074	79	−2
	5	7.91	7.69	0.119	21	0.097	64	−3
4A	53	5.83	5.98	0.157	20	0.124	70	−2
4C	Preoperatively	4.63	6.17	0.093	31	0.047	78	−9
	5	5.19	4.62	0.134	31	0.072	51	−1
4D	Preoperatively	4.11	4.15	0.170	18	0.140	52	
	5	5.35	4.12	0.110	23	0.131	55	−5
4E	Preoperatively	8.37	10	0.060	29	0.062	100	−5
	2	10.4	9.16	0.072	22	0.062	100	−0.2
5F	12	2.65	3.64	0.072	26	0.051	72	−3
6A	50	4.49	6.05	0.059	33	0.049	55	−4
6C	60	3.45	3.12	0.136	19	0.096	50	−4
6D	21	2.16	2.37	0.352	20	0.230	59	−0
8A	4	5.82	9.06	0.085	17	0.045	90	−4
	8†	8.07	7.64	0.073	17	0.047	70	−3
	12	7.63	11.1	0.054	15	0.059	64	−0.2
10A	48	5.18	4.83	0.083	24	0.069	60	−4

* Mean of 14 young normal subjects studied in this laboratory

† Following second operation

TABLE 4

MEAN VALUES FOR MAXIMAL BREATHING CAPACITY, RESTING VENTILATION, AND EXERCISE VENTILATION*

	Maximal Breathing Capacity		Resting Ventilation		Exercise Ventilation	
	Per Cent Predicted	Number of Cases	L/Minute	Number of Cases	L/Minute	Number of Cases
Preoperatively.....	73	(10)	10.3	(11)	40.7	(9)
Postoperatively.....	75	(10)	10.2	(11)	37.9	(9)

* Based on the cases in which both pre- and postoperative studies are available

did not suggest that the diminution in vital capacity was directly proportional to the extent of the resection.

Complete pre- and postoperative studies of *pulmonary compliance and resistance* are available in 4 cases. In addition, studies were made before and after the second operation in *Case 8A*. In 7 additional cases postoperative studies only were performed (table 3).

If the value of 3 cm. per liter per sec. is regarded as the maximal normal nonelastic resistance, each of the 4 patients studied had elevated values prior to operation. Following surgery there appeared to be a slight further rise in all of these cases. In some the resistance values were extremely high.

In the 4 patients studied preoperatively the *compliance* of the lung was normal in 2 and reduced in 2. Following surgery there was a slight and probably insignificant reduction in 2 while in one (*Case 4C*) there was actually a slight increase. The patient (*Case 6D*), the oldest subject in the series, is of interest, as his compliance twenty-one months after operation was 0.35 liter per cm. of water. Of the 12 patients studied for the first time after operation, pulmonary compliance was considered to be definitely reduced in 7. In these, tachypnea caused a further fall in most instances.

The average intra-esophageal pressure at the end of expiration relative to atmospheric pressure varied between 0 and −9 cm. of water. In only 2 cases was this level unusually low (−9 cm. of water) and in one of these a value of −1 cm. was obtained following surgery five months later (*Case 4C*). Intra-esophageal pressure was recorded as atmospheric in *Case 6D*, in which the compliance value suggested loss of pulmonary elasticity.

In every case the preoperative values for *maximal breathing capacity* were low. The reduction was frequently very marked and quite out of proportion to the extent of the lesion. Operation was in some instances followed by an immediate fall in maximal breathing capacity, but with the passage of time it nearly always reverted to its previous level, an occasional patient showing what was probably a significant improvement. In those patients measured by a comparable technique, the final postoperative value was surprisingly close to the preoperative value (table 4). The remaining patients were tested on a relatively high resistance circuit and showed the same trend.

Values for *resting ventilation* were elevated in 2 of the patients tested preoperatively, while hyperventilation in response to a work load of 300 k. gm. per min. was evident in 6 cases. Postoperative values appeared strikingly similar to those recorded preoperatively. In no case was a really significant increase recorded, while 2 of the patients with extensive resections decreased their exercise ventilation by 20 per cent postoperatively.

Pre- and postoperative *oximetric studies* were completed in 12 subjects (figure 1). In normal subjects at this altitude there is rarely a drop of more than 3 per cent and never more than 5 per cent following the standard Hugh-Jones exercise test set at 300 kg. m. per min. (14). In the present study, 4 subjects showed a fall in excess of 5 per cent preoperatively, while another 4 subjects showed falls

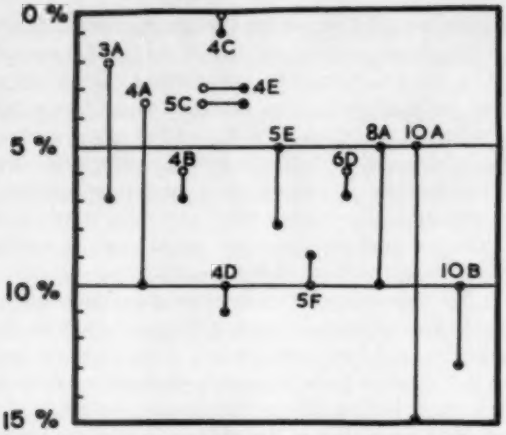

FIG. 1. Percentage fall in arterial oxygen saturation during a standard effort test. Cases are designated *3A*, *5A*, *et cetera* according to the number of segments removed at operation (*see* table 1). For each case the open circle indicates the fall in percentage arterial oxygen saturation during the standard effort test before operation, the closed circle representing the same value at the most recent postoperative investigation. Thus *Case 8A* showed a fall of 5 per cent before operation and 10 per cent after operation. *Case 4E*, on the other hand, showed no change postoperatively.

of 3 to 5 per cent. Following surgery, the general trend was toward a greater fall on standard effort, 11 patients exceeding the 5 per cent limit. No patient showed a significantly smaller fall following surgery, nor in the 4 cases followed for a sufficient time was there any suggestion of improvement with the passage of time.

Distribution of inspired air as recorded by the *lung clearance index* was abnormal in 10 of the subjects before surgery. In 6 of these it appeared to improve significantly postoperatively, and in no case was there a major deterioration in this aspect of lung function.

DISCUSSION

It is apparent from the above results that a degree of hyperinflation was present in the subjects before surgical intervention took place (residual volume and functional residual capacity above predicted values). Surgical resection of tissue resulted in a reduction in values for residual volume and functional residual capacity in the immediate postoperative period. With the passage of time, however, further expansion occurred until the final values approached and, in some cases, exceeded those obtained preoperatively. When it is recalled that prediction figures were based on normal values for both lungs, it is apparent that postoperative hyperinflation of the remaining lung was invariable. It also appeared that this postoperative inflation was more marked with increasing age of the subject.

To what extent was there a concomitant loss of respiratory function? Sub-

jectively, 5 patients reported reduction of breathlessness, 6 reported a slight increase, and the remainder noticed no change in this symptom. Vital capacity, already low in 17 cases preoperatively, was further reduced by surgery in only 10 subjects. With the passage of time, however, there was a marked tendency for vital capacity values to return to and, in some cases, even exceed the preoperative levels. Only one of the patients tested a year after surgery had maintained a definite reduction. Breathing work against nonelastic resistance was elevated preoperatively and a further small elevation resulted from surgery in the 5 cases in which pre- and postoperative values could be compared. The high preoperative values could be the result of raised tissue viscance or air-way resistance or both, but the postoperative increase was almost certainly a result of reduction in the total cross-sectional area of the respiratory ducts.

Pulmonary compliance values were low in 7 of the 12 cases studied postoperatively, although it is difficult to be certain to what extent these low values were the result of surgery. A further fall in compliance as a result of tachypnea in 5 patients suggests that inequality of distribution may have been at least partly responsible (15). This finding contrasts with the series of subjects studied following pneumonectomy for carcinoma by McIlroy and Bates (16). In their patients low compliance was demonstrated conclusively to result from overdistension and was quite uninfluenced by tachypnea. Furthermore, the lower compliance values were not obviously related to low levels of absolute esophageal pressure as might be anticipated if hyperinflation were the cause (16). Finally, in the 5 cases in which the effects of surgery could be observed no major reductions in compliance were evident. It is believed that the low values for compliance in the present series are thus most probably due to loss of functioning lung tissue (due to the disease process) and that surgery causes a slight further fall. The conclusion appears justified that, although a considerable increase of work against elastic resistance may result from the removal of a whole functioning lung (16), compliance is probably not greatly reduced as a result of resection of largely nonfunctioning segments in bronchiectasis. This appears to be true even when the number of segments removed is equivalent to a whole lung. Irrespective of any changes in respiratory work, however, values for maximal breathing capacity appear to have been improved by surgery rather than the reverse; and it is probable that factors such as reduced toxicity from infection, increased muscle power, and a reduction of the amount of secretion in the respiratory tract account for improvement of these values.

Intrapulmonary distribution of air in the lungs tended to improve following surgery. Values for resting ventilation and ventilatory response to effort were substantially unchanged apart from strikingly improved values in 2 cases. By contrast there was a tendency to slightly greater anoxemia in response to effort, presumably the result of diminished diffusing capacity consequent on the loss of lung tissue.

It is reasonable to conclude that in the present series, despite undeniably poor function preoperatively and in spite of the development in most subjects of marked distension of the remaining lung following surgery, no major loss of

function was observed in any of the tests performed. The only adverse long-term effect noted was a slightly increased arterial anoxemia on effort. This conclusion corresponds to the fact that in all but 5 of the patients no subjective deterioration was experienced, and in 2 of these there was marked residual disease to account for persistent symptoms. It thus appears that extensive segmental resection may safely be undertaken in cases of bronchiectasis even in the presence of considerable reduction in pulmonary function.

These conclusions do not correspond closely with the conclusions of other workers. Smith, Siebens, and Storey (17) who examined a large group of bronchiectatic patients pre- and postoperatively found that surgery produced a loss of function in proportion to the extent of the resection. This finding was based on a fall in vital capacity and maximal breathing capacity measured, however, in most cases within four months of the operation. In the light of the improvement observed in the present cases with the passage of time after surgery, the short observation period of Smith and associates probably explains this discrepancy.

Mannix and associates (5) made postoperative studies of only 8 survivors following surgery for bilateral bronchiectasis and found considerable impairment of function (reduced maximal breathing capacity, increased residual volume, resting ventilation and impaired mixing). The presence of all of these factors in many of the present cases preoperatively, however, suggests that it would be inadvisable to ascribe any of them to the surgical intervention in a study in which only postoperative testing was done.

On the more general question of whether hyperinflation of the lung may of itself be detrimental to function there is no clear agreement. McIlroy and Bates (16), in a study of 10 patients after pneumonectomy for bronchial carcinoma, concluded that in the presence of hyperinflation there was a much reduced compliance associated with a low esophageal pressure, which they believed was the cause of increased dyspnea. Cournand and associates (4) made a detailed study of ventilation-perfusion relationships in a series of 9 cases studied at an average interval of seventy-seven months after pneumonectomy. They found distension with a reduction of maximal breathing capacity, a tendency to hyperventilate, and a slightly abnormal fall of arterial oxygen on effort. There was no evidence, however, that the distension caused the other functional disturbances Moreover, the abnormalities associated with mild distension (reduced percentage of effective pulmonary blood flow and reduced maximal breathing capacity) were different from those associated with more marked inflation (reduced effective alveolar ventilation with normal maximal breathing capacity and normal percentage of effective pulmonary blood flow). If distension alone were the cause of postoperative functional disturbances, they might be expected to be similar in character although different in degree in the patients with mild and severe postoperative distension, respectively. Moreover, compared with the average maximal breathing capacity in a group of patients soon after pneumonectomy, the average maximal breathing capacity was reduced less despite greater distension. Likewise, the breathing reserve was larger on standard effort than in the less inflated group studied soon after surgery. Cournand and associates

concluded, however, that distension was harmful and even recommended thoracoplasty when "pneumonectomy is complicated by pulmonary distension." Gaensler and Strieder (6), in a study of 40 subjects up to two-and-a-half years after pneumonectomy, found that overdistension of the remaining lung was not associated with deterioration of function as assessed by maximal breathing capacity, vital capacity, exercise, and distributional factors.

Comparison between the effects of resection of whole functioning lungs and diseased largely nonfunctioning segments should probably not be carried too far. The indirect evidence of the present study, however, confirms the conclusions of Gaensler and Strieder in so far as it has failed to find evidence that overdistension has had a detrimental effect on function. The evidence suggests rather that the slight depression of lung function which was observed following resection (anoxemia on effort and increased nonelastic resistance) was more likely the result of loss of lung tissue and was not related to postoperative hyperinflation.

Summary

Bronchiectasis of any degree of severity may result in marked impairment of lung function. Consequently both pre- and postoperative studies are necessary to determine the functional effects of the operation. Results of postoperative studies alone must be interpreted with caution.

Studies performed in the immediate postoperative period will not reflect the eventual functional state of the lung. In the months following resection of bronchiectatic segments, two progressive changes were observed, namely, increasing inflation and progressive improvement of maximal breathing capacity.

In conservative surgery, that is, restriction of surgery to the diseased lung even when this is extensive, the adverse effects on lung function were small in the series examined. Surgery resulted in no adverse effect on maximal breathing capacity; gas distribution was somewhat improved; there was no increase in ventilatory response to effort. However, following surgery there was a slight increase in nonelastic resistance, some decrease of vital capacity, and a tendency to increased anoxia on effort in some subjects.

Considerable hyperinflation of the remaining lung was the rule in this as in other series. Hyperinflation may be anticipated to be more marked in older age groups. No evidence was found that the degree of hyperinflation observed here had any directly adverse influence on lung function as measured by a battery of lung function tests, or on the patient's symptoms postoperatively.

It is suggested that extensive segmental resection may probably be safely undertaken even in the presence of considerable reduction of pulmonary function.

Sumario

La Función Respiratoria Consecutivamente a la Resección Segmental del Pulmón por Bronquiectasia

Sea cual fuere su gravedad, la bronquectasia puede ocasionar notable deterioro de la función pulmonar. Por consiguiente, se necesitan estudios pre- y postoperatorios para determinar los efectos funcionales de la operación. Por sí solos, los resultados de los estudios postoperatorios deben ser interpretados con cautela.

Los estudios ejecutados en el período postoperatorio inmediato no reflejarán el estado funcional definitivo del pulmón. En los meses consecutivos a la resección de segmentos bronquiectáticos, observáronse dos alteraciones progresivas, a saber, hiperinflación y mejoramiento gradual de la capacidad respiratoria máxima.

En la cirugía conservadora, es decir, limitación de la intervención a la porción enferma del pulmón, aun siendo ésta extensa, los efectos adversos sobre la función pulmonar fueron pocos en la serie estudiada. La cirugía no produjo efecto adverso sobre la capacidad respiratoria máxima; la distribución de gases mejoró algo; no hubo aumento de la respuesta ventiladora al esfuerzo. Sin embargo, después de la cirugía hubo un leve aumento de la resistencia inelástica, alguna disminución de la capacidad vital y tendencia, en algunos sujetos, a aumento de la anoxia tras el esfuerzo.

En esta, así como en otras series, hubo, por regla general, considerable hiperinflación del pulmón restante. Cabe esperar que la misma sea más acentuada en los grupos de edad mayor. No se descubrieron signos de que la intensidad de la hiperinflación observada ejerciera el menor efecto adverso directo sobre la función pulmonar, medida esta con una combinación de pruebas de la función pulmonar, o sobre los síntomas del enfermo postoperatoriamente.

Sugiérese que probablemente puede emprenderse sin temor la resección segmental extensa aun cuando existe considerable reducción de la función pulmonar.

Resume

La fonction respiratoire après résection segmentaire du poumon pour bronchectasie

La bronchectasie, quel que soit son degré de gravité, peut entraîner une insuffisance fonctionnelle du poumon. En conséquence des recherches pré et post-opératoires sont nécessaires pour déterminer les effets de l'intervention sur la fonction. Les résultats de l'étude post-opératoire seule ne doivent être interprétés qu'avec prudence.

Les recherches effectuées dans la période succédant immédiatement à l'opération ne reflèteront pas l'état fonctionnel ultérieur du poumon. Dans les mois qui suivent la résection des segments bronchectasiques, deux modifications progressives se manifestent, c'est-à-dire l'accroissement de l'inflation et l'amélioration progressive de la capacité respiratoire maxima.

Lorsque la chirurgie est conservatrice, c'est-à-dire que lorsque la résection est restreinte au segment affecté, même si elle est extensive, les effets nocifs sur la fonction respiratoire étaient réduits dans les séries qui furent étudiées. L'intervention chirurgicale n'a pas eu d'action nocive sur la capacité respiratoire maxima; la répartition des gaz était légèrement améliorée; la résponse de la ventilation à l'effort n'était pas augmentée. A la suite de l'opération, il s'est produit une légère augmentation de la résistance non-élastique, une certaine réduction de la capacité vitale et une tendance à l'accroissement de l'anoxie à l'effort chez quelques sujets.

Dans cette série, comme dans les autres, l'hyperinflation du poumon conservé était constante. On peut prévoir que l'hyperinflation sera plus marquée parmi les groupes de sujets âgés. Il n'a été obtenu aucune preuve permettant de démontrer que le degré de l'hyperinflation observée exerçait une influence nocine directe sur la fonction du poumon, déterminée par une série de tests fonctionnels, ou sur les symptômes présentés par le malade après l'opération.

L'article suggère qu'il est possible de pratiquer une résection segmentaire étendue avec sécurité, même en présence d'une réduction considérable de la fonction pulmonaire.

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CYSTIC CAVITIES IN PULMONARY TUBERCULOSIS TREATED WITH ISONIAZID[1]

VLADIMIR ALTMANN AND RAPHAEL M. DIAZ

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INTRODUCTION

Puzzling cystlike defects have been observed in resected lung specimens or in lungs of patients who died of pulmonary tuberculosis at Sea View Hospital since the latter part of 1952. Their possible relation to modern chemotherapy and especially to treatment with isoniazid derivatives was first suggested in a report on a patient examined at autopsy (1). Later a few reports on this subject appeared in the literature (2–10). A preliminary report on the pertinent pathologic material studied at Sea View Hospital has been previously published (11). Since that time, the total number of similar cases at this institution have almost tripled.

Several editorials appeared in the past, in widely read medical publications, which mentioned these defects in the lungs as being a part of the changing pathology of tuberculosis (12, 13). Since these attested to considerable interest in the subject, and because there appeared to be a certain confusion among some clinicians with respect to the meaning and practical importance of the recently observed cystic structures, the decision was made by the present writers to report their observations on this material. The conclusions reached in this study are based on gross and microscopic features; laboratory examinations of sputum; the observation that cystic cavities have been encountered much more frequently in tuberculous lungs since the introduction of isoniazid; and the clinical experience of frequent remissions which in a previous era used to be considered only exceptional. Most of these topics will be discussed in more detail below.

MATERIAL

The present study is based on pathologic examinations of lung specimens removed by surgery and lungs of patients who died of pulmonary tuberculosis and were examined at autopsy. The lung specimens were distended to the original size by injection of sufficient amounts of a 1:9 mixture of formalin in alcohol through the main bronchus. Usually several sections were obtained for microscopic study from significant lesions, especially from cavity walls or cystic structures. These sections were embedded in the routine manner in paraffin and were stained with hematoxylin and eosin. Special staining procedures were used very rarely. Only those lung specimens were included in this study which came from patients treated with isoniazid. All specimens contained cavitary lesions and were examined during the four and one-half year period from June, 1952, to December, 1956. Specimens from patients not showing cavitary disease or not treated with isoniazid were excluded. This material is represented by 157 surgically resected lung specimens and the lungs of 91 patients on whom an autopsy was performed.

OBSERVATIONS

For the sake of clarity, it seems advisable to mention first the main criteria used for healed cavities, bronchogenic structures, and emphysematous cysts.

[1] From the Department of Pathology, Sea View Hospital, Staten Island, New York.

Healed cavities (figures 1, 2, and 3) occur in locations customarily occupied by tuberculous cavities; they have definite, regular walls which are fibrous; they have thicker walls than are usually seen in emphysematous cysts, and are not associated with any significant gross emphysematous changes in other portions of the lung; they show absence of recognizable bronchial elements, such as smooth muscle, et cetera. These criteria offer only circumstantial evidence. Direct proof is impossible because there is nothing specific about the fibrous tissue that forms the wall of an open healed cavity. It is exactly for this reason that the original diagnoses were tentative, as can be seen by glancing at table 1.

Bronchogenic defects show residual structures of bronchial walls, i.e., smooth muscle, glands, cartilage, et cetera. The bronchial type of epithelium, on the other hand, does not per se necessarily denote bronchial origin but may represent, in some cases, only an extension of the epithelium lining contiguous bronchi.

Emphysematous cysts have, as a rule, very thin walls; they are associated with obviously emphysematous lesions in adjacent and other portions of the lung; often they have walls with irregular outlines.

The conclusions that can be drawn from this study using the above criteria may be summarized as follows:

There seem to be no specific changes in the lungs attributable to isoniazid or peculiar to this drug. The healing processes are the same, as they may occur with any type of treatment and sometimes in spontaneous remissions. Only the rate, extent, and frequency of some favorable responses appear to be influenced by the isoniazid.

The frequency of cystic cavities in patients with cavitary pulmonary tuberculosis treated with isoniazid is significantly greater than in those who were not given the drug. Among the lung specimens of 248 patients there were 14 cystic cavities, whereas in a group of 193 patients with similar cavitary pulmonary tuberculosis, treated with streptomycin but not with isoniazid, only one cystic structure was present.

The cysts can be interpreted to represent healed cavities. This may be so despite the experience that the observed cysts were frequently associated with persisting

FIG. 1 (*Case 5*). Portion of lung containing multiple large cystic cavities.

FIG. 2 (*Case 6*). Lung containing a large cystic cavity.

FIG. 3 (*Case 6*). Low-power photomicrograph of the wall of cystlike healed cavity.

TABLE 1

Case	Treatment	Duration of Tuberculosis	Sputum	Gross Examination of the Specimen	Microscopic Examination	Conclusion on the Cysts
		years				
1. F. M. (52-276)	Isoniazid—9 months Iproniazid—4 months Streptomycin—5 months Pneumothorax	3	Sputum initially positive for tubercle bacilli; later negative for tubercle bacilli	*Left lung*—Tuberculous cavity in apex and lower lobe; caseous foci; also smooth-walled defects in lower lobe 1, 1.5 cm. in diameter.	Smooth-walled defects in lower lobe have fibrous wall showing only very slight scattering of lymphocytes but with no evidence of active tuberculosis; also tuberculous cavities and caseous foci in lung.	Possibly healed cavity
2. P. J. (52-285)	Isoniazid—5 months Streptomycin—10 months PAS—5 months	1	Sputum always positive for tubercle bacilli except for two months before pneumonectomy	*Left lung*—Large smooth-walled defect in apex resembling cyst, having a diameter of about 5 cm. Two smaller tuberculous cavities in upper lobe; few small subacinar lesions in lower lobe.	The cystlike structure in the apex has fibrotic wall slightly infiltrated with lymphocytes. It shows no evidence of necrosis. Other cavities are tuberculous.	Possibly healed cavities
3. M. R.	Isoniazid—5 months Streptomycin—several months PAS—several months Pneumoperitoneum	2	Sputum alternately positive and negative for tubercle bacilli	*Left lung*—Tuberculous cavities with inspissated contents; caseous foci; also a small smooth-walled defect in basal portion.	The small cystlike defect has a fibrous wall in which there is only slight residual active inflammation, entirely nonspecific. There are focal collections of epithelium-like cells along the inner surface; tuberculous granulation tissue in the wall of the other cavities.	Possibly healed cavity

4. M. B. (198-53)	Isoniazid—4 months Streptomycin—4 months	1½	Sputum initially positive for tubercle bacilli; later for several months negative for tubercle bacilli	*Left lung*—Markedly fibrous and contraction of the upper lobe; smooth-walled cavity in upper lobe, about 3 cm. in diameter, and a smaller one in lower lobe; few encapsulated caseous foci in both lobes.	The smooth-walled structures have fibrous wall only slightly infiltrated with lymphocytes. Only a few epithelium-like cells along inner surface.	Possibly healed cavities
5. R. S. (216-53)	Isoniazid—7 months Streptomycin—7 months PAS—7 months	3	Only initial sputum positive for tubercle bacilli; subsequent sputum persistently negative for tubercle bacilli	*Left lung*—System of large intercommunicating cystlike defects in both lobes. Their lining is almost entirely smooth and shiny. Only very occasional small rough lesions are present. Only few acinous foci in lung.	The cystlike structures have a fibrous wall containing only few lymphoid cells. Only very rare small necrotic lesions interrupt the continuity of the fibrous wall; occasional small epithelioid tubercles in other sections.	Possibly healed cavities
6. W. S. (271-53)	Isoniazid—7 months Streptomycin—18 months	3½	Sputum always positive for tubercle bacilli	*Left lung*—Large cystlike cavity in upper lobe having a diameter of 12-14 cm. Small hemorrhages in its wall; dilated bronchi and caseous foci of various sizes in lower lobe.	The large defect has a thick fibrous wall showing only few inflammatory cells. There is partial epithelization in areas opening into a medium-sized bronchus.	Possibly healed cavity
7. T. D. (102-54)	Isoniazid—18 months Streptomycin—18 months	1½	Initial sputum and gastric cultures negative for tubercle bacilli; later sputum concentrate positive for tubercle bacilli	*Left upper lobe*—Emphysema in apex. Defect in apex 1.2 cm. in diameter having smooth inner surface and fibrous wall; no definitely tuberculous large cavity in upper lobe; caseous foci.	Defect has thin fibrous wall, lined with mesothelial-like cells. Practically no inflammatory process in wall; also encapsulated caseous foci present in lobe	Cavity pathogenesis undetermined, possibly healed cavity
8. F. D. (245-54)	Isoniazid—2 years Streptomycin—2 years PAS	2	Sputum always positive for tubercle bacilli	*Right upper and middle lobes*—Cystlike defect in apex 6-7 cm. in diameter; also definitely tuberculous large cavity in upper lobe; caseous foci.	Cystlike structure has fibrous wall, with no evidence of epithelization; no necrosis in its wall; also tuberculous cavity; encapsulated caseous foci.	Possibly healed cavity

TABLE 1—CONTINUED

Case	Treatment	Duration of Tuberculosis	Sputum	Gross Examination of the Specimen	Microscopic Examination	Conclusion on the Cysts
		years				
9. A. P. (73-55)	Isoniazid—10 months PAS—10 months Streptomycin—10 months Pneumothorax Pneumoperitoneum	4	Sputum initially positive for tubercle bacilli; for last ten months negative for tubercle bacilli	*Left lung*—Large cystlike defect occupying two-thirds of upper lobe, about 9 cm. in diameter, not communicating with large bronchi; no definite active gross tuberculosis in lung.	Cystlike structure has fibrous wall. Nonspecific inflammatory process in adjacent tissue. A few calcified foci in wall may be healed tuberculosis. Chronic pneumonitis with fibrosis; occasional cholesterol granuloma; chronic bronchitis.	Possibly healed cavity
10. H. M. (82-55)	Isoniazid—20 months Streptomycin—20 months	4	Initial sputum positive for tubercle bacilli; later persistently negative for tubercle bacilli	*Right upper lobe*—Marked pleural thickening; wedge-shaped scar; emphysematous defects (?). One large collapsed, cystlike structure with smooth lining; only rare gray foci of healed tuberculosis.	Large cystlike structure has fibrous wall lined with mesothelial-like cells. No definite tuberculosis in wall; focal scarring—probably healed tuberculosis; small and large cysts, origin undetermined.	Cysts—pathogenesis undetermined
11. P. W. (162-55)	Isoniazid—8 months Streptomycin—8 months PAS—2 weeks	2	Sputum alternately positive and negative for tubercle bacilli	*Left lung*—Large defect in upper lobe, grossly free of tuberculosis, with fibrous wall; fibronodular tuberculosis in lingula.	Large defect has fibrous wall. Nonspecific chronic inflammatory infiltration in adjacent tissue; inspissated cavity in lingula; fibronodular and acinous tuberculous foci.	Possibly healed cavity

12. J. F. (A13-55)	Isoniazid—15 months Streptomycin—15 months PAS—1 year Penicillin—15 days Chlortetracycline—15 days Oxytetracycline—17 days Pneumothorax—1 year	5	Sputum alternately positive and negative for tubercle bacilli	*Right lung*—Several tuberculous cavities; also a large cyst-like defect 8 cm. in diameter possibly pleurogenic. *Left lung*—Large cavity; recent hemorrhage into cavity; acinous nodose foci.	Smooth-walled structure in right lower lobe has thick fibrous wall blending with pleura—origin undetermined. Inspissated cavity in lingula, left lung; tuberculous cavity in right upper lobe and left upper lobe.	Cyst—pathogenesis undetermined
13. E. R. (A26-55)	Isoniazid—2 years Streptomycin—2 years PAS—3 years Equilite®—1 year WIN® 5211—1 year Oxytetracycline Phrenic crush Pneumothorax Pneumoperitoneum	5	Sputum always positive for tubercle bacilli	*Right lung*—Large tuberculous cavity; next to it a smooth-walled defect 2 cm. in diameter. *Left lung*—Tuberculous cavities and noncavitary tuberculosis.	Small defect has fibrous wall and along its inner surface there are heaped-up mononuclear cells of uncertain origin.	Cyst—pathogenesis undetermined
14. H. H. (A39-56)	Isoniazid—3 years PAS—3 years Streptomycin—3 years	17	Sputum alternately positive and negative for tubercle bacilli	*Right lung*—Much emphysema and bronchiectasis; some thin-walled defects. *Left lung*—Tuberculous cavity in upper lobe. Bronchiectasis and cystlike space in lower lobe, 2.5 cm. in diameter.	Defect in right lower lobe has the structure of cyst with fibrous wall. The cavity in left upper lobe shows nonspecific ulceration. All of these may be cavities in various stages of healing.	Cyst—pathogenesis undetermined

active tuberculous lesions and often even with frankly tuberculous cavities. This can readily be appreciated by glancing at the table summarizing the most important clinical and pathologic features in the 14 cases of cystic cavities.

This disturbing fact seems to require brief comment. Not only does the life history of tuberculous infection in general present numerous paradoxical phenomena, but it is also the daily experience of clinicians and pathologists alike to be able to observe in individual cases evidence of progression of the disease side-by-side with various degrees of healing. As a matter of fact, the coexistence of such opposing processes forms the very essence of the variegated picture of chronic pulmonary tuberculosis.

Twenty other lung specimens were examined during the same four-and-a-half-year period which on gross examination showed essentially similar cystic defects, but microscopic study revealed that these were quite definitely not healed cavities. Bronchiectasis was the nature of these cysts in 11 cases, only partly healed tuberculous cavity in 5, active tuberculous cavity in one, emphysematous cyst in 2, and pleurogenic cyst in one case.

Discussion

Examples of healing tuberculous cavities, although rare, were occasionally observed even in the days before specific chemotherapy. Auerbach (14) stated that in 2,000 autopsy cases from this period there was only one example of a completely healed cavity of this nature among all of the tuberculous lungs examined. In 193 lung specimens from patients having cavitary pulmonary tuberculosis and treated with streptomycin, one case was recorded at Sea View Hospital as presenting a similar structure. This suggests that as a consequence of streptomycin treatment a partial increase occurred in the frequency of these lesions. The phenomenon in the respective cases may be related to the process of healing of bronchocavitary junctions, as pointed out by Auerbach (14). A wide, persistently patent bronchocavitary junction would favor rapid evacuation of the necrotic material from the cavity and gradual conversion of its wall into nonspecific granulation tissue and ultimately into ordinary fibrous tissue.

The further marked increase in the frequency of healed cystic cavities in the lungs of patients who were on isoniazid–streptomycin therapy can be plausibly explained if one supplements the observations made on the healing of bronchocavitary junctions with such ideas concerning the interaction of these therapeutic agents as expressed by Russel, Dressler, Middlebrook, and Denst (13). According to these writers, streptomycin alone is usually not sufficiently effective within cavities containing large amounts of necrotic material because this material contains a considerable concentration of desoxyribonucleic acid, supposedly an antagonist of streptomycin. Isoniazid, on the other hand, is not inhibited in its therapeutic action by this material. The chief role of streptomycin would appear to be to combat the isoniazid-resistant tubercle bacilli that emerge within the cavity as a result of prolonged isoniazid therapy. This would occur in favorable cases during a period when much of the desoxyribonucleic acid has been already

eliminated together with the necrotic material. Thus the postulated neutralization of streptomycin by this substance would no longer occur or would be greatly reduced. Actually, all cases of cystic cavities in the material herein presented were those of patients treated with isoniazid along with streptomycin. It has been shown convincingly that isoniazid–streptomycin is superior to streptomycin alone, but the hypothesis of Russell and associates need not necessarily be correct. Other explanations may be offered. Therefore, a certain doubt may remain in the minds of some students of this subject whether the cysts observed actually represented open healed cavities. There is no absolute proof for this. In spite of the fact that they occurred often in locations usually occupied by tuberculous cavities and that they fulfilled such criteria for open healed cavities as those postulated by Melzer (15), there remains a possibility that the pathogenesis of some of these cysts is different.

The interpretation of these cysts as healed cavities is to a great extent dependent on the clinical observations, often mentioned at conferences, of unusually rapid healing and at times even complete disappearance of cavitary lesions from the roentgenogram shortly after the institution of isoniazid therapy. It is most probable that the actual frequency of these cysts is considerably greater than would appear from this study. Any pathologic material represents usually only material from those selected patients which for one reason or another did not respond satisfactorily to treatment. It is for this reason that only a certain trend can be demonstrated in such material. As a result of increased frequency in the incidence of cysts in tuberculous patients, there emerges often enough the problem of how to interpret thin-walled defects persisting in the roentgenograms of patients whose sputum has become negative for tubercle bacilli. Impressions gained from participation in medical-surgical conferences, in which such problems have been extensively discussed (16), and the writers' own experience with the pertinent pathologic material resulted in the crystallization of the following ideas in connection with cystlike cavities:

> Thin-walled, regular defects with smooth outlines observable on roentgenograms may be healing or healed tuberculous cavities, but their true nature cannot be reliably established by roentgenographic examination alone. The presence or absence of other lesions suggestive of tuberculosis, together with the information whether the sputum is positive or negative for tubercle bacilli, always influences opinions concerning these defects.
>
> In any patient with a cystic defect in the lung, in which the sputum only occasionally contains tubercle bacilli, there is a possibility that the cysts might not be active tuberculous cavities and that the specimens of infectious sputum in such cases might be due only to active noncavitary lesions. These cysts, consequently, may become a source of much confusion and of erroneous interpretation. Conservative therapy for prolonged periods is probably advisable in most of these instances, especially in the absence of roentgenographic evidence of spread of disease. When the disappearance of tubercle bacilli from the sputum has been maintained for twelve months or longer, these cysts, in most cases, prove to be free of active tuberculosis. This seems to be so at least with the relatively numerous cases observed for several years in Sea View Hospital (17).

Summary

Cystic defects in the lungs of patients treated with isoniazid-streptomycin can be interpreted frequently as healed tuberculous cavities. There is usually, however, only circumstantial clinical and pathologic evidence for such a conclusion. The occurrence of these cysts in clinical practice is probably considerably greater than is noted in pathologic material. Their importance is therefore more significant than would appear from a pathologic study alone.

Roentgenographic appearance, results of sputum examinations, and the possibility of other tuberculous lesions shown in the roentgenograms have to be considered together in order to arrive at practical conclusions regarding the possible true nature of these cysts. In the presence of sputum positive for *M. tuberculosis*, inactive cysts may be erroneously considered to be active tuberculous cavities, resulting in an improper choice of treatment.

Sumario

Las Cavernas Quísticas de la Tuberculosis Pulmonar Tratadas con Isoniacida

Los nichos quísticos en los pulmones de enfermos tratados con isoniacida-estreptomicina pueden pasar frecuentemente por cavernas tuberculosas cicatrizadas. Sin embargo, no suele haber más que datos clínicos e histopatológicos circunstanciales para llegar a esa conclusión. La incidencia de esos quistes en la práctica clínica es probablemente mucho mayor que la observada en el material histopatológico. Su existencia es, por lo tanto, más importante que lo que indica el estudio patológico solo.

Hay que considerar conjuntamente el aspecto radiográfico, los resultados de los exámenes del esputo y la posibilidad de otras lesiones tuberculosas mostradas en las radiografías a fin de llegar a conclusiones prácticas acerca de la posible verdadera naturaleza de estos quistes. Cuando el esputo es positivo para *M. tuberculosis*, puede considerarse erróneamente que los quistes son cavernas tuberculosas activas, conduciendo esto a la elección de un tratamiento impropio.

Resume

Les excavations kystiques dans la tuberculose pulmonaire traitée par l'isoniazide

Les lésions kystiques siégeant dans les poumons de malades traités par l'association isoniazide-streptomycine peuvent être souvent interprétées comme représentant des cavernes tuberculeuses cicatrisées. Habituellement, il n'y a que des preuves indirectes cliniques et anatomo-pathologiques en faveur de cette conclusion. L'occurrence de ces kystes observés en clinique est probablement beaucoup plus fréquente que ne le révèlent les pièces pathologiques. Leur importance est donc plus significative que l'étude anatomo-pathologique seule ne permet de le constater.

Les images radiologiques, les résultats de l'examen des crachats et la possibilité de la présence d'autres lésions tuberculeuses visibles sur les radiogrammes doivent être considérés en bloc, de manière à parvenir à une conclusion sur la vraie nature de ces kystes. En présence de crachats "positifs" pour le *M. tuberculosis* des kystes stabilisés pourraient être considérés par erreur comme des cavernes tuberculeuses en activité, ce qui aurait pour résultat le choix d'un traitement inapproprié.

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EFFECTS OF ISONIAZID PROPHYLAXIS ON THE TUBERCULIN RESPONSE AND THE LOCAL LESION FOLLOWING BCG VACCINATION OF ADULTS[1]

LEO S. PALITZ

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Introduction

Intense interest in the possible prophylactic effect of isoniazid on tuberculous hypersensitivity was a natural outcome of its demonstrated effectiveness on the course of the disease itself. This interest was stimulated by the report of Robinson, Meyer, and Middlebrook (1) of reversion of a positive tuberculin skin test to negative in four of six infants less than two years of age with negative chest roentgenograms after treatment with isoniazid for six to seven months in a dosage of 8 mg. per kg. of body weight per day. Before treatment these infants gave positive Mantoux responses to a dilution of 1:1,000 Old Tuberculin (OT) and after treatment were negative to OT in a dilution of 1:100. One of these children had also received streptomycin.

The same writers reported the essential ineffectiveness of isoniazid in its ability to reverse a positive Mantoux reaction in seven infants less than one year of age who had roentgenographic evidence of tuberculosis. Likewise, Hewell and Suyemoto (2) and Criep and Levine (3) found no reversing effect of isoniazid on the positive Mantoux reactions of tuberculous patients. Isoniazid has also been shown to be ineffective in reversing the positive tuberculin test following BCG vaccine inoculation. Aronson, Taylor, and Kirk (4) showed that there was respectively no significant statistical difference in the behavior of the tuberculin test and the healing of BCG vaccine-induced ulcers between control subjects and isoniazid-treated subjects in each of two groups with different levels of sensitivity: (*1*) those BCG-vaccinated for the first time, and (*2*) of even lower hypersensitivity, those BCG-vaccinated from one to five times previously.

Two studies specifically designed to analyze under special conditions developing hypersensitivity in negative reactors have recently been reported. One, which is part of a larger study by Palmer, Ferebee, and Hopwood (5) on prevention of experimental tuberculosis in guinea pigs, showed the effects of several regimens of continuous and intermittent isoniazid administration started forty-eight hours before a large intraperitoneal challenge dose of virulent organisms was inoculated and continued up to twenty-two weeks after inoculation. The continuous regimens and the larger-dosage regimens were most effective in depressing the level of hypersensitivity, although generally unable to suppress the development of allergy.

The other study was by Choremis, Liacacos, Allamanis, Zoumboulakis, and Kourti (6) and was concerned with the effects of isoniazid on the local ulcer, the

[1] From the Tuberculosis Division, Veterans Administration Hospital, Northport, Long Island, New York.

axillary lymph node, and the tuberculin skin reaction in children one to fifteen years of age. Isoniazid in dosage of 4 to 6 mg. per kg. of body weight per day was administered four days before, simultaneously, and one week after BCG inoculation, to children who had reacted negatively to 5 units of purified protein derivative (PPD) tuberculin eight days before BCG vaccination. Effectiveness in preventing adenitis and depressing the size of the local reaction was noted. Most remarkable was the prevention of the development of a positive Mantoux test at eleven weeks after BCG inoculation in twenty-six of twenty-nine children who were inoculated for the first time, while all thirteen control subjects developed positive skin tests regardless of whether they were previously inoculated. The test dose was 10 units of PPD and the results were confirmed by employing a sensitive Koch phenomenon test.

The purpose of the present study is to analyze the effects of a moderately large dose of isoniazid upon the local reaction and tuberculin skin test in adult subjects when administered before inoculation of a standard dose of BCG vaccine and upon the skin test after withdrawal of the drug.

Materials and Methods

Seventy-four male adults—69 white and 5 non-white—with a diagnosis of schizophrenia, on several wards of the Veterans Administration Hospital at Northport, Long Island, completed the first phase of the study in 169 days under the conditions planned for the various study and control groups. Forty-nine subjects—45 white and 4 non-white—were tested at the end of the second phase (following withdrawal of the drug) at 491 days after BCG inoculation. All subjects were tested with 0.1 mg. of OT at the onset, and were divided at random into two groups, one of which received BCG vaccine.

The BCG vaccine group was inoculated with 0.1 ml. intradermally in the deltoid region of the left arm. The vaccine was the intradermal variety (Lot #486) prepared by Dr. Joseph D. Aronson of the Henry Phipps Institute, Philadelphia, Pennsylvania.

The BCG vaccine-inoculated group consisted of 50 reactors, 48 negative and 2 positive. Of the 48 negative reactors:

36 were started on isoniazid one to 14 days before BCG vaccine inoculation.

30 of these (averaging 29.6 years of age) received the drug continuously for 266 days.

6 others (averaging 30.2 years of age) had isoniazid stopped at the time of BCG vaccine administration. In 4 of these subjects (to be referred to as the "interrupted-isoniazid" group) chemotherapy was re-started 18 days after inoculation and was continued for 266 days without interruption in 2, and interruptedly in the remaining 2.

12 (averaging 31.5 years of age) did not receive isoniazid at any time.

The 2 positive reactors were studied in order to obtain corroborative evidence of Koch phenomena which might be expected to be present in some degree in any group of adult negative reactors chosen on the basis of a tuberculin skin test with 0.1 mg. of OT. On this basis, several subjects were eliminated from the study.

Isoniazid was started in a total daily dosage of 600 mg. (approximately 10 mg. per kg.) between 7 and 21 days after the original Mantoux test was read. The 30 subjects who received isoniazid without interruption had an average body weight of 153.9 pounds. The 12 persons who did not receive isoniazid had an average body weight of 144 pounds. The 6 subjects for whom isoniazid was halted at the time of BCG inoculation had an average body weight of 152.7 pounds.

BCG vaccine was administered 21 days after the original Mantoux test was read.

Examinations were made of the BCG nodule at 4, 18, 36, 64, 106, and 169 days.

At 36 and 64 days, Mantoux tests with 0.1 mg. of OT were performed on two small separate sets of subjects, each of which contained representatives of the three groups mentioned above. At 106 days a majority of the BCG vaccine-inoculated persons were tested with 1.0 mg. of OT, and at 169 days the entire population was tested with both strengths.

All tests were made on the left forearm and were read at 72 hours except when otherwise noted. A positive Mantoux test was considered to be an area of induration of 5 mm. or more in diameter at 72 hours.

The group which did not receive BCG vaccine consisted of 24 negative reactors:

12 persons started isoniazid at the same time as the 36 members of the BCG vaccine-inoculated group.

6 (averaging 34.8 years of age) received isoniazid continuously for 266 days. This group had an average body weight of 155 pounds.

6 (averaging 31.2 years of age) had the drug withdrawn on the day BCG vaccine was inoculated. This group had an average body weight of 160.3 pounds.

12 persons (averaging 37.3 years of age) did not receive isoniazid at any time. This group had an average body weight of 145.8 pounds.

The several non-BCG groups were observed in order to study the tuberculin responses in developing natural infection during the period of this experiment. An unusually large response to tuberculin in the BCG vaccine-inoculated subjects could be considered evidence of superimposed natural infection.

At 64 days Mantoux tests were performed with 0.1 mg. of OT on several members of the continuous-isoniazid and non-isoniazid groups; at 106 days, with 1.0 mg. of OT on several members of the continuous-isoniazid group; and at 169 days, with both strengths of OT on the entire non-BCG population.

At 491 days after BCG inoculation (225 days after discontinuation of chemoprophylaxis) a final test was performed with both strengths of tuberculin on the entire available population—49 subjects—representing all groups.

Results

The effects of isoniazid on newly inoculated live BCG cells were exerted at the portal of entry. A study of local reactions at 4, 18, and 36 days after BCG vaccine inoculation is represented in table 1.

The BCG vaccine nodule in negative reactors and under uncomplicated conditions slowly increases in size for about one month after inoculation and then slowly recedes. The subjects who did not receive isoniazid reacted normally in this respect: the nodules reached their largest size at 36 days. The continuous-isoniazid group, however, showed the effects of isoniazid administration from the onset. In this group, the nodules grew more slowly during the first 18 days, and at 36 days had shown considerable shrinkage. In addition, there was significantly less ulceration in this group. The local lesions in the group in which isoniazid was discontinued at the time of inoculation grew most rapidly in the early stages. However, when isoniazid was resumed in half of this group at 18 days after BCG vaccine inoculation, a significant shrinkage was noted in the nodules.

The effect of isoniazid on the developing tuberculous hypersensitivity may be measured by the responses to the intradermal skin test. In table 2 are revealed the results of such findings and related local reactions in two separate small groups at 36 and 64 days.

Continuous isoniazid administration affected the conversion rate as early as

TABLE 1

LOCAL REACTIONS AT 4, 18, AND 36 DAYS AFTER BCG VACCINE INOCULATION

Group	At 4 Days				At 18 Days				At 36 Days			
	Number	Mean Size	Number Ulcerated	Per cent Ulcerated	Number	Mean Size	Number Ulcerated	Per cent Ulcerated	Number	Mean Size	Number Ulcerated	Per cent Ulcerated
Continuous isoniazid	30	4.8	0	0	30	5.1	0	0	29	4.7	14	48.2
No isoniazid	12	5.3	0	0	12	5.8	0	0	11	6.8	8	72.7
Interrupted isoniazid*	7	4.7	0	0								
					4	6.3	0	0	4	6.3	3	75.0
					4	6.8	2	50.0	4†	5.8	4	100.0

* Isoniazid discontinued at time of BCG vaccine inoculation.

† Isoniazid re-started after 18-day examination.

36 days after BCG vaccine inoculation. While only 2 of 12 of the continuous-isoniazid group reacted at this time, 3 of 4 non-isoniazid subjects showed conversion of the tuberculin reaction to positive. The 2 subjects who comprised the interrupted-isoniazid group likewise showed a conversion of the tuberculin reaction to positive. Additional evidence of the suppressive effect of the continuous administration of isoniazid may be seen in the striking difference between the mean sizes of the intradermal reactions of the positive reactors of the continuous-isoniazid group and of the non-isoniazid group. Here again, the results in the interrupted-isoniazid group were of the order of the results in the non-isoniazid group.

At 64 days the effectiveness of continuous isoniazid on the "conversion" rate was still evident. One subject in the interrupted-isoniazid group showed conversion of the reaction to positive. The 2 non-BCG control groups continued to be negative to 0.1 mg. of tuberculin.

At 106 days after BCG vaccine inoculation, 37 subjects were tested with 1.0 mg. of OT, and at 169 days the entire group of 72 negative reactors were retested with 0.1 mg. and 1.0 mg. of OT simultaneously in the left and right forearms, respectively. The results are set forth in tables 3 and 4.

The striking feature of the tuberculin tests in the continuous-isoniazid group at 106 and 169 days was the significant increase in incidence of positive reactors to 1.0 mg. of tuberculin compared to the response to 0.1 mg. Thus at 169 days, while the percentage of positivity to 1.0 mg. had almost doubled over the response to 0.1 mg. in the non-isoniazid group, it had quadrupled in the continuous-isoniazid group. Furthermore, while the total amount of tuberculous allergy had increased somewhat more than sixfold in response to 1.0 mg. of OT over that of the response to 0.1 mg. in the continuous-isoniazid group, it had increased less than threefold in the non-isoniazid group.

In the interrupted-isoniazid group, no allergy could be evoked at the 0.1 mg. level while 1.0 mg. produced positive reactions in 100 per cent of those tested.

TABLE 2

INTRADERMAL AND RELATED LOCAL REACTIONS IN TWO GROUPS AT 36 AND 64 DAYS AFTER BCG VACCINE INOCULATION
Test Dose 0.1 Mg. OT; Reading at 72 Hours

	Group	Number	Mean Size of Intradermal Reaction (Total)	Negative Reactors			Positive Reactors				
				Number	Mean Size of Local Reaction	Per Cent Ulcerated	Number	Per Cent	Mean Size of Intradermal Reaction	Mean Size of Local Reaction	Per Cent Ulcerated
At 36 days, 18 subjects	BCG, continuous isoniazid	12	1.0	10	4.3	50.0	2	16.7	6.0	5.0	100.0
	BCG, no isoniazid	4*	10.8	1	7.0	0	3	75.0	14.3	7.0	100.0
	BCG, interrupted isoniazid†	2	11.5	0	—	—	2	100.0	11.5	6.5	100.0
At 64 days, 23 subjects	BCG, continuous isoniazid	7	4.9	5	2.8	40.0	2	28.6	15	6.0	100.0
	BCG, no isoniazid	6‡	11.7	1	6.0	100.0	5	83.3	14	5.6	60.0
	BCG, interrupted isoniazid†	1	10.0	0	—	—	1	100.0	10	5.0	100.0
	No BCG, continuous isoniazid	6	0	6	—	—	0	—	—	—	—
	No BCG, no isoniazid	3	0	3	—	—	0	—	—	—	—

* Includes one subject to whom isoniazid was given 1 to 14 days before BCG inoculation and then discontinued.
† Isoniazid discontinued at the time of BCG vaccine inoculation and resumed after 18 days.
‡ Includes 2 subjects to whom isoniazid was given 1 to 14 days before BCG inoculation and then discontinued.

TABLE 3

INTRADERMAL AND RELATED LOCAL REACTIONS AT 106 DAYS
Test Dose 1.0 Mg. OT; Reading at 96 Hours

Group	Number	Mean Size of Intradermal Reaction (Total)	Mean Size of Local Reaction (All healed)	Negative Reactors		Positive Reactors			
				Number	Mean Size of Local Reaction	Number	Per cent	Mean Size of Intradermal Reaction	Mean Size of Local Reaction
BCG, continuous isoniazid	24	8.4	4.0	4	3.5	20	83.3	10.1	4.1
BCG, no isoniazid	6*	13.2	4.9	0	—	6	100.0	13.2	4.9
BCG, interrupted isoniazid†	4‡	11.0	6.0	1	6.0	3	75.0	14.7	6.0
No BCG, continuous isoniazid	3	0	—	3	—	0	0.0	—	—

* Includes one subject to whom isoniazid was discontinued when BCG vaccine was inoculated.

† Isoniazid discontinued at time of BCG vaccine inoculation and resumed after 18 days.

‡ Includes 2 subjects for whom isoniazid was continued with interruptions as follows: one missed 36 doses between the seventy-eighth and ninetieth days; the other missed 81 doses between the thirty-eighth and sixty-fifth days.

It may be remembered that at 36 and 64 days the several subjects tested in the interrupted-isoniazid group were positive to 0.1 mg. of OT.

It is clear that chemoprophylaxis can significantly suppress the level of tuberculous allergy, although the hypersensitive state develops in 80 per cent of the subjects. In addition, there is evidence derived from a test at 491 days that development of hypersensitivity was only delayed in some of the nonreacting 20 per cent of the subjects.

Of interest is the apparent suppressive effect of isoniazid on the allergy associated with natural infection. In a very small number of natural converters, the total amount of allergy evoked by 1.0 mg. of OT in the non-BCG continuous-isoniazid group was 3.75 times the amount elicited by 0.1 mg.; while, in the non-BCG non-isoniazid group, 1.0 mg. of OT could only elicit slightly less than 2.8 times the amount evoked by 0.1 mg. of OT. It would be difficult, however, to decide whether this represents new or old infection. The natural conversion rate of 16.7 per cent to 0.1 mg. of OT represents an increase in allergy during the experimental period. In view of the fact that the test dose at the onset of the experiment was only 0.1 mg. of OT, one cannot be certain whether this allergy represents new or old infection, since some of these subjects may have been originally positive to 1.0 mg. of OT. It is of interest to note that one natural converter (under continuous isoniazid)—of the 2 who were positive to 1.0 mg. of OT at 169 days—was negative to the same test dose at 106 days.

TABLE 4

INTRADERMAL AND RELATED LOCAL REACTIONS AT 169 DAYS
Test Doses 0.1 Mg. OT and 1.0 Mg. OT; Reading at 72 Hours

Group	Number*	Mean Size of Local Reaction	0.1 Mg. OT					1.0 Mg. OT				
			Mean Size of Intradermal Reaction (Total)	Number Negative	Number Positive	Per cent Positive	Mean Size of Mantoux Positive Reactors	Mean Size of Intradermal Reaction (Total)	Number Negative	Number Positive	Per cent Positive	Mean Size of Mantoux Positive Reactors
BCG, continuous isoniazid	30	3.4	1.5	24	6	20.0	7.5	9.2	6	24	80.0	11.4
BCG, no isoniazid	14†	5.1	5.2‡	6	7	53.8	9.6	14.3	0	14	100.0	14.3
BCG, interrupted isoniazid§	4‖	5.3	0	4	0	0.0	—	17.0	0	4	100.0	17.0
No BCG, continuous isoniazid	6	—	0.8	5	1	16.7	5.0	3.0	4	2	33.3	9.0
No BCG, no isoniazid	18#	—	1.4	15	3	16.7	8.7	3.9	13	5	27.8	14.0

* Skin test results in the 2 originally positive reactors are not shown.

† Includes 2 subjects for whom isoniazid was discontinued when BCG vaccine was inoculated.

‡ One skin test result with 0.1 mg. of OT not recorded—average of 13.

§ Isoniazid discontinued at time of BCG vaccine inoculation and resumed after 18 days.

‖ Includes 2 subjects for whom isoniazid was continued with interruptions as follows: one missed 36 doses between the seventy-eighth and ninetieth days; the other missed 81 doses between the thirty-eighth and sixty-fifth days.

Includes 6 subjects for whom isoniazid was discontinued when BCG vaccine was inoculated.

There is, in addition, little evidence of superimposed natural infection on any of the BCG-inoculated groups. Only one person (in the non-isoniazid group) developed large enough reactions to suggest this possibility—26 and 31 mm. to 0.1 and 1.0 mg. of OT, respectively.

Following the test at 169 days, isoniazid prophylaxis was discontinued in the entire group. Four hundred and ninety-one days after BCG inoculation, 49 subjects representing all of the original groups were retested with 0.1 mg. and 1.0 mg. of OT simultaneously. At this time all but 3 of the subjects were free of the drug for 225 days. The exceptions are noted in table 5.

At the 491-day test, the BCG non-isoniazid group had developed important losses of hypersensitivity to both strengths of tuberculin. At the 0.1 mg. level the incidence of positive reactors dropped from 53.8 to 14.3 per cent, and at the 1.0 mg. level, from 100 to 71.4 per cent. On the other hand, the BCG continuous-isoniazid group revealed relatively small losses in allergy. At the 0.1 mg. level the

INTRADERMAL REACTIONS AT 491 DAYS
Test Doses 0.1 Mg. OT and 1.0 Mg. OT; Reading at 72 Hours

Group	Number	0.1 Mg. OT					1.0 Mg. OT					Comments on Individual Changes in Response to Both Strengths of Tuberculin Between 169 and 491 Day Tests
		Mean Size of Intradermal Reaction (Total)	Number Negative	Number Positive	Per Cent Positive	Mean Size of Positive Reactors	Mean Size of Intradermal Reaction (Total)	Number Negative	Number Positive	Per Cent Positive	Mean Size of Positive Reactors	
BCG, continuous isoniazid	23*	1.1	21	2	8.7	7.0	7.0	5	18	78.3	8.7	12 were unchanged 11 were changed as follows: 1 gained allergy to 0.1 mg. of OT 1 gained to 1.0 mg. of OT 4 lost to 0.1 mg. of OT 4 lost to 1.0 mg. of OT 1 lost to both strengths
BCG, no isoniazid	7†	3.0	6	1	14.3	15.0	9.7	2	5	71.4	12.6	2 were unchanged 5 were changed as follows: 3 lost allergy to 0.1 mg. of OT 2 lost to 1.0 mg. of OT
BCG, interrupted isoniazid‡	4§	5.25	2	2	50.0	10.5	11.0	0	4	100.0	11.0	2 were unchanged 2 were changed as follows: 2 gained allergy to 0.1 mg. of OT
No BCG, continuous isoniazid	1‖	0	1	0	0.0	—	11.0	0	1	100.0	11.0	1 was unchanged
No BCG, no isoniazid	14#	3.8	9	5	35.7	12.6	8.5	6	8	57.1	14.6	8 were unchanged 6 were changed as follows: 1 lost allergy to 0.1 mg. of OT 1 gained to 0.1 mg. of OT 2 gained to 1.0 mg. of OT 2 gained to both strengths

* Two subjects had no drug for 265 days.
† Includes one subject for whom isoniazid was discontinued when BCG vaccine was inoculated.
‡ Isoniazid discontinued at time of BCG inoculation; resumed at 18 days.
§ Isoniazid resumed at 18 days; 2 uninterrupted, 2 interrupted as noted in table 4.
‖ No isoniazid for 300 days.
Includes 5 subjects for whom isoniazid was discontinued when BCG vaccine was inoculated.

percentage of positive reactors dropped from 20.0 to 8.7, and at the 1.0 mg. level there was only a minimal change from 80.0 to 78.3.

In the BCG interrupted-isoniazid group there was an increase in hypersensitivity from 0.0 to 50.0 per cent at the 0.1 mg. level, while the response to 1.0 mg. remained constant at 100 per cent.

Analysis of the individual responses reveals an actual increase of allergy in several of the subjects. The loss of significant amounts of allergy in the BCG non-isoniazid group was an unexpected development and reflects in some degree the low incidence (53.8 per cent) of positive reactors to 0.1 mg. of OT at 169 days. Nevertheless, it does appear significant that the BCG continuous-isoniazid group as well as the interrupted-isoniazid group showed only small losses of allergy and even actual gains.

The non-BCG non-isoniazid group continued to show an increasing incidence of natural infection, but it seems unlikely that allergy of natural infection was superimposed on any of the BCG vaccine-inoculated groups since a Mantoux response of 20 mm. was the highest recorded reaction in these groups.

Discussion

It is clear that continuous chemoprophylaxis can hinder the development of the vaccination lesion and significantly suppress the level of tuberculous allergy. Its effect on the local lesion begins immediately after inoculation and is followed by a rather strikingly suppressive action after the eighteenth day under the conditions of the experiment, even in instances in which it has been restarted on the eighteenth day after inoculation. The effectiveness persists throughout the experiment with respect to the differences between the two major groups—the BCG continuous-isoniazid and the BCG non-isoniazid. The local lesions of the BCG interrupted-isoniazid group assume equivocal positions, being smaller than those of the non-isoniazid group at the 36- and 64-day examinations, and larger at the 106- and 169-day examinations.

The marked suppression of allergy at the lower testing level and the striking reversal of the tuberculin responses of the drug-treated group at the 1.0 mg. testing level require consideration. Generally, under similar conditions, fewer living or dead cells produce smaller Mantoux responses and smaller local lesions. Under prophylactic chemotherapy, therefore, it is likely that the altered responses are due to a smaller number of living cells. However, the sudden destruction of large numbers of living cells in inoculation experiments of this type (in which organisms are protected by intracutaneous tissues) may provide elements of allergic responses and local lesions due to dead organisms. The extremely small mean Mantoux response to 0.1 mg. of OT and the "reduction in the production of allergy out of proportion to the reduction in size of vaccination lesions" (7) suggest an accumulation of dead organisms. The marked reversal of allergic response to 1.0 mg. of OT, however, to a point not very far behind that of the normal BCG response, suggests the presence of living and multiplying organisms.

The living organisms are probably in a variety of metabolic states. The bacteria in the dormant state are not very active and do not increase their population, although they can be recovered and counted, while those in the latent state

cannot be located or cultured by current methods (8). The dormant organisms can probably produce adequate amounts of allergy. The latent variety, however, is apparently affected much more profoundly. It is possible that they are unable to produce allergy while in that state, although several months after withdrawal of drug they appear able to produce hypersensitivity, suggesting re-establishment of multiplication. As for the resistant variety, two recent studies have shown that *in vitro*-developed isoniazid-resistant strains of BCG produced a degree of allergy of no statistical difference from that produced by the susceptible parent strain (9, 10). Under *in vivo* conditions, however, chemoprophylaxis suppresses allergy; but it is not known whether, under these same conditions, organisms develop resistance. Indeed, in experiments to date the bacilli have shown a decided tendency to remain susceptible.

It is worth noting that an attenuated organism such as BCG has survived eight months of chemoprophylaxis.

The amount of immunity that might develop as a result of the presence of the remaining living organisms is a key question and a practical problem. Dubos and Pierce (11) have thrown light on the question in animal experiments which relates specifically to problems of immunity They conclude that "antituberculous immunity by BCG vaccination is the outcome of the antigenic response to bacillary material having two different origins: (*a*) the bacilli present in the vaccine preparation; (*b*) the bacilli that multiply *in vivo* after infection." They speculate that, although the intradermal route of inoculation is different from that used in mice experiments, the usual amounts of vaccine inoculated in humans (converting from mouse weight) were small (of the order of 10^{-4} to 10^{-5} ml. of culture per mouse) and, therefore, their multiplication *in vivo* was necessary in order to stimulate development of immunity. This is in contrast to the evidence that a large dose of bacillary material (even of dead organisms) "can provide outright an intense antigenic stimulus and elicit immunity even though the vaccinating bacilli do not have a chance to multiply *in vivo*." It must be pointed out, however, that the dose of 5 mg. of isoniazid daily for a 15 to 20 gm. mouse is about 25 times the dosage used in this experiment. It is not considered likely that interference with multiplication was as profound as was demonstrated in the Dubos and Pierce experiments.

The recent studies discussed above and others suggest the following as being applicable to humans. It appears probable that virulent organisms will be able to gain entry into the body by inhalation despite chemoprophylaxis. Having gained a foothold, they will probably be prevented from producing progressive disease (12). Allergy levels will certainly be depressed, but it is not clear whether hypersensitivity can be completely suppressed. This may be determined by the number and frequency of inhalation of organisms.

Conclusions of the same order can be drawn from inoculation experiments so far as preventing progressive disease is concerned (13); but in this type of study, as in the current BCG experiment, hypersensitivity develops in significant although diminished amounts. All evidence points to increase of allergy in experiments of both types when chemoprophylaxis is withdrawn.

The increase in allergy after withdrawal of drug in animal inhalation ex-

periments is followed by active and progressive disease when the original infecting organism is virulent. If in infants under chemoprophylaxis a small number of organisms gain entry, the likelihood of progressive disease following withdrawal of drug might be small. But if large numbers gain a foothold, active primary disease might well be the outcome. It would seem, therefore, that, in infants in whom chemoprophylaxis might be considered a useful measure, the optimal period of drug administration might extend beyond the age at which the serious sequelae of first infection would be likely to occur; that is, about five years of age.

BCG vaccine would appear to be especially useful in combination with chemoprophylaxis since allergy and immunity develop under this combined therapy. The immunizing vaccine could be either a standard dose of isoniazid-resistant organisms or a somewhat larger dose of isoniazid-susceptible bacteria. The protection provided by the vaccine a few months after inoculation would, of course, be of a different nature from that provided by chemoprophylaxis. It is the result of the sensitizing and immunizing properties of the vaccine, and once inoculated, provides varying degrees of protection, probably for years.

Summary

Isoniazid chemoprophylaxis in a continuous dosage of 10 mg. per kg. per day reduces the size of the local reaction, decreases the incidence of ulceration with much of the effect coming between the eighteenth and thirty-sixth days, and exerts a significant suppressive effect on the level of tuberculous allergy following the introduction in adult humans of an average immunizing dose of BCG vaccine. This suggests that the multiplication of living cells is altered by isoniazid chemoprophylaxis under these conditions.

Nevertheless, 80 per cent of the drug-treated subjects in the experiment developed tuberculous hypersensitivity as revealed by responses to 1.0 mg. of tuberculin. Suppressive effects of the same order were noted when the drug was stopped at the time of BCG vaccine inoculation and was re-started after 18 days.

In the drug-treated BCG vaccine-inoculated groups, allergy levels were maintained with relatively little loss (several actually gained allergy) following the withdrawal of the drug, in contrast to the large loss of hypersensitivity in the non-drug-treated groups. It is possible that renewed multiplication of BCG cells was responsible for the individual gains in allergy.

The remarkable ability of an attenuated organism such as BCG to "persist" under strong drug attack is noted.

Sumario

Efectos de la Profilaxis con Isoniacida sobre la Reacción a la Tuberculina y la Lesión Local Consecutiva a la Inoculación de BCG en Sujetos Adultos

La quimioprofilaxis con isoniacida a una dosis continua de 10 mg. por kg. al día reduce el tamaño de la reacción local, disminuye la incidencia de ulceración (sobreviniendo gran parte del efecto entre el décimooctavo y el vigésimosexto días) y ejerce un importante efecto supresor sobre el nivel de la alergia tuberculosa consecutiva a la introducción en adultos humanos de una dosis inmunizante media de vacuna BCG. Esto sugiere que la multiplicación de células vivientes es alterada por la quimioprofilaxis con isoniacida en estas condiciones.

Sin embargo, 80 por ciento de los sujetos tratados con la droga en el experimento manifestaron hipersensibilidad tuberculosa según revelaron las respuestas a 1.0 mg. de tuberculina. Notáronse efectos supresivos del mismo orden cuando se suspendió la droga al hacer la inoculación de BCG y se reinició al cabo de dieciocho días.

En los grupos tratados con la droga e inoculados con BCG, se mantuvieron los valores de alergia con pérdida relativamente escasa (en varios hasta aumentó la alergia) después de la supresión de la droga, en contraposición a la gran pérdida de hipersensibilidad en los grupos que no fueron tratados con la droga. Es posible que la renovada multiplicación de las células de BCG fuera la causa de los aumentos de alergia en algunos casos.

Señálase la notable capacidad de un microbio atenuado, tal como BCG, para "persistir" bajo poderoso ataque medicamentoso.

Resume

Effets prophylactiques de l'isoniazide sur la réaction à la tuberculine et sur la lésion locale consécutive à la vaccination par le BCG chez l'adulte

La chimioprophylaxie par l'isoniazide à la dose continue de 10 mg/kg par jour réduit les dimensions de la réaction locale, abaisse l'incidence de l'ulcération (une grande partie de l'effet se manifeste entre le dix-huitième et le trente-sixième jour) et réduit de façon significative le degré de l'allergie tuberculeuse qui succède à l'inoculation immunisante d'une dose moyenne de vaccin BCG. Ces notions indiquent que dans ces conditions la multiplication des cellules vivantes est altérée par l'administration d'isoniazide à titre prophylactique.

Néanmoins, chez 80% des sujets traités par ce composé au cours de l'expérimentation il s'est développé une allergie tuberculeuse qui fut décelée par la réaction à 1 mg de tuberculine. Des effets d'inhibition du même ordre furent observés quand l'administration de l'isoniazide était interrompue au moment de l'inoculation du BCG et reprenait au bout de dix-huit jours.

Dans les groupes inoculés ayant été traités par le composé, le degré d'allergie s'est maintenu sans réduction sensible (en fait, il a parfois augmenté) lorsque l'administration du composé a cessé, à l'encontre d'une réduction considérable de l'allergie dans les groupes non-traités. Il est possible qu'une reprise de la multiplication des cellules BCG soit responsable du gain individuel en allergie.

La propriété remarquable que possède un germe atténué, comme le BCG, de "persister" sous l'attaque d'une drogue puissante est signalée.

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THE BACTERIOLOGY OF TUBERCULOUS LESIONS RESECTED AFTER CHEMOTHERAPY[1,2]

ROBERT G. BLOCH, ABRAHAM S. BUCHBERG, SOLBERT PERMUTT, AND GERTRUDE NEUMANN

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INTRODUCTION

The study of the pathology and bacteriology of tuberculosis has received great impetus through the development of resectional surgery. This type of surgery has made possible for the first time the detailed pathologic and bacteriologic study of tuberculous lesions obtained from patients who have not died of their disease; it facilitates the investigation of the effect of modern chemotherapy on tuberculous lesions and, most important, on the tubercle bacilli.

The present investigation was undertaken to compare the experience of the writers with that of other investigators and to add to the available data a few new and detailed observations. The results were gained through the study of the following important problems: the bacteriology of cavernous and closed lesions of different sizes, the correlation of bacteriologic findings in resected specimens with sputum findings on hospital admission and on preoperative tests, the comparison of bacteriologic findings in different lesions obtained from the same resected specimen, and the correlation of bacteriologic findings in resected lesions of various types and sizes with the duration of preoperative chemotherapy.

The study was carried out on 400 different tuberculous lesions obtained from 81 patients on whom segmental resection, lobectomy, or pneumonectomy was performed. All patients had received prolonged preoperative chemotherapy. Triple-drug therapy with streptomycin, isoniazid, and PAS was used for advanced bilateral disease whenever the possibility of surgical treatment at a later date seemed dubious initially. In patients in whom the possibility of resection seemed likely, two-drug therapy was instituted, retaining a third drug for the pre- and postoperative periods. The purpose of this regimen was to ensure effective therapy after the possible emergence of bacilli resistant to the drugs initially used. In a few cases pyrazinamide and viomycin were used. No attempt was made to correlate the findings with any particular chemotherapeutic regimen except for the duration of treatment. It was believed that the results should be taken as they presented themselves in a patient population which in any tuberculosis hospital, for a variety of medical and surgical considerations, requires different combinations and dosages of drugs.

MATERIALS AND METHODS

Each specimen was dissected under sterile precautions within twenty-four hours after surgery by an approach through the bronchial tree, whenever possible, as well as through

[1] From the Division of Pulmonary Diseases, Montefiore Hospital, New York, New York.

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incisions from the periphery of the lung. A new set of instruments was used for each dissecting operation. Several lesions or parts of lesions from each specimen were removed, opened, and placed in separate containers. From all of the larger lesions the essential parts, and especially the caseous content, were taken for study. In all specimens in which small nodular lesions were found in fair numbers, two or more such nodules were removed.

The material is divided into two main groups, open cavities and closed lesions, with subdivisions of each variety into three groups according to size. Cavities were differentiated into the following sizes: small size, 3 to 10 mm. in diameter; medium size, 10 to 30 mm.; large size, more than 30 mm. Closed lesions were divided into small size, 3 mm. or less; medium size, 3 to 10 mm.; and large size, more than 10 mm.

All lesions and caseous materials removed from cavities were ground in a mortar with the addition of small amounts of Dubos medium broth (without Tween® and albumin). Smears were made from caseous material directly when possible, or else from homogenate. Approximately 0.5 ml. of homogenate was inoculated into each of 3 tubes of Löwenstein (Jensen) medium, 2 tubes of Dubos medium (Tween-albumin), and 2 tubes of charcoal agar medium. The use of charcoal agar medium was discontinued after about one year because it was found that in no instance were cultures positive on charcoal media when no growth was found on Löwenstein and Dubos media.

All Löwenstein medium cultures were read weekly and not discarded before six months Dubos medium cultures were subcultured to Löwenstein medium after four weeks and again after three months and were then discarded.

In order to check on the reliability of the dissecting and cultural technique, control cultures were made from seemingly uninvolved parts of the specimen whenever possible; often this was difficult, and in a few cases impossible, because of the great extent of the pulmonary involvement. The latter fact explains that 2 of 36 such controls were positive for tubercle bacilli on microscopy and one on culture. In addition, cultures were taken intermittently from nontuberculous resected specimens (mostly neoplastic). None of 12 such specimens yielded tubercle bacilli.

Results

Pathologic observations were limited to gross inspection of the specimen and, therefore, cannot add to the detailed histologic observations reported by other investigators. The study of the effect of chemotherapy on cavities consisted of scrutiny of the content and of the wall of the cavity after removal of its caseous contents.

In general, the comparison of the present material with autopsy experience during the pre-chemotherapeutic era did not convey the impression that chemotherapy has as much influence on cavity behavior as has been claimed by a number of investigators. There seemed to be almost as much liquefaction of caseous material as used to be seen in untreated cavities and consequently as much—but hardly more—tendency to inspissation. The occurrence of "open healing" which now is reported so often as a result of chemotherapy was not a prominent observation. In only 4 cavernous lesions were the walls smooth and apparently cleansed of necrotic material. The scrapings from 2 of these cavities, however, were positive for tubercle bacilli.

The essential bacteriologic data obtained in this investigation are expressed in a number of tables. For greater clarity the contents of each table or group of tables are discussed briefly following presentation of the data.

As may be seen in table 1, the majority of lesions were closed ones; small tubercles made up nearly one-third of the total material (31.5 per cent). The

TABLE 1

TYPES AND NUMBERS OF LESIONS FROM 81 PATIENTS

Type of Lesion	Number	Per Cent	Total Percentage
Cavernous			
Small size, 3 to 10 mm.	53	13.2	40.0%
Medium size, 10 to 30 mm.	62	15.5	
Large size, more than 30 mm.	45	11.3	
Closed Caseous			
Small size, 3 mm. or less	126	31.5	60.0%
Medium size, 3 to 10 mm.	75	18.8	
Large size, more than 10 mm.	39	9.7	
Total	400		

TABLE 2

DIAGNOSIS OF CAVITIES

Comparison of Roentgenographic Diagnosis (including tomography) and Pathologic Findings		
Cavity diagnosed by roentgenogram; confirmed in the specimen	62	Correct roentgenographic diagnosis 89%
No cavity diagnosed by roentgenogram; no cavity found in specimen	10	
Cavity diagnosed by roentgenogram; not confirmed in specimen	8	Incorrect roentgenographic diagnosis 11%
No cavity diagnosed by roentgenogram; cavity present in specimen	1	
Total	81	100%

overwhelming majority of even the smallest tubercles showed central caseation, often only of pinpoint size. The pre-existence of a cavity which by inspissation developed into one of the larger closed lesions could be established in a considerable number of cases. Open cavities accounted for 40 per cent; closed caseous lesions, for 60 per cent of the total material.

As a sidelight, the comparison of preoperative roentgenographic interpretation, including tomography, with pathologic findings is presented in table 2. The clinical diagnosis of cavitation proved correct in 89 per cent of the patients. Incorrect diagnosis of excavation was due mostly to the presence of localized emphysema and in a very few cases to bronchiectasis.

In table 3 the type and size of lesions are compared with the bacteriologic findings obtained from their contents. The differentiation into four categories is that usually employed, namely, positive for tubercle bacilli on microscopy and culture; negative on microscopy and positive on culture; positive on microscopy and negative on culture; and negative for tubercle bacilli by both microscopy and culture. Much attention has been paid by others to the discrepancy between

TABLE 3

RELATIONSHIP OF TYPE AND SIZE OF LESIONS AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Type of Lesion	Positive Microscopy and Positive Culture		Negative Microscopy and Positive Culture		Total Number with Positive Culture		Positive Microscopy and Negative Culture		Negative Microscopy and Negative Culture		Total Number with Negative Culture		Total
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	
Cavernous													
Small size	12	22.7	6	11.3	18	34.0	14	26.4	21	39.6	35	66.0	53
													100%
Medium size	31	50.0	4	6.5	35	56.5	11	17.7	16	25.8	27	43.5	62
													100%
Large size	25	55.6	6	13.3	31	68.9	9	20.0	5	11.1	14	31.1	45
													100%
All sizes	68	42.5	16	10.0	84	52.5	34	21.2	42	26.2	76	47.5	160
Closed caseous													
Small size	24	19.0	23	18.3	47	37.3	28	22.2	51	40.5	79	62.7	126
													100%
Medium size	16	21.4	11	14.6	27	36.0	24	32.0	24	32.0	48	64.0	75
													100%
Large size	14	35.9	2	5.2	16	41.1	10	25.6	13	33.3	23	58.9	39
													100%
All Sizes	54	22.5	36	15.0	90	37.5	62	25.8	88	36.7	150	62.5	240

findings on microscopic examination and culture, especially to the seemingly incongruous result of a direct smear positive for acid-fast bacilli, followed by a negative culture. The present writers believe that this point has been overemphasized since it expresses an underestimation of the effect of chemotherapy which can render tubercle bacilli incapable of multiplication without destroying them morphologically. In the present study, the tubercle bacilli which could be cultured from resected material regardless of the results of direct microscopic examination were the chief target of interest because of their clinical importance. Consequently, it seemed advisable to report the cultures positive for tubercle bacilli together in a separate column regardless of the results obtained by microscopy. Such a column is included in all tables.

There was a significant difference in the cultural results from the caseous contents of open cavities, depending upon their size; the large ones yielded more than twice as many positive cultures (68.9 per cent) as the small ones (34.0 per cent), with the medium-sized cavities registering in the middle (56.5 per cent). In the closed caseous lesions, size was of no significant influence on cultural growth. However, there was a significant difference between the number of closed lesions of large and medium size which were positive for tubercle bacilli both on microscopy and culture. This could be explained by the greater possibility

of the larger closed lesions resulting from recent inspissation of cavities which showed an abundance of positive findings on both microscopy and culture. The percentage of cavities and closed lesions of all sizes which were positive only by microscopy did not differ significantly (21.2 per cent and 25.8 per cent); the total number of cultures positive for tubercle bacilli was higher for cavities (52.5 per cent) than for closed lesions (37.5 per cent).

Canetti (1) reported 75 per cent of positive findings from open cavities by computing the findings of eight different writers, and the enigma of the closed lesion has been investigated by a number of writers. The findings differ widely, apparently due to the scarcity of material in some studies, the different mode employed in selecting the lesions, or to differences in the handling of the resected material and in bacteriologic technique. Canetti (2) quotes four reports in which the isolation of tubercle bacilli from nodular lesions by culture or inoculation ranged from 7.4 to 52 per cent. Wier (3) reported 30 per cent of more than 800 closed lesions as positive for tubercle bacilli. Hobby and associates (4) found 64 per cent of closed lesions positive for tubercle bacilli without differentiation as to their size; D'Esopo (5) reported positive findings in 20 per cent of nodules corresponding in size (10 mm. or less) to the 201 nodules in the present study which were found to be positive for tubercle bacilli in 37 per cent.

In tables 4*A* and 4*B*, the bacteriologic findings in the specimens are compared with the patient*s*' admission and preoperative sputum findings. The percentage of patients whose sputum converted from positive on admission to negative preoperatively was smallest in the group in which the resected specimens showed lesions positive for tubercle bacilli on both microscopy and culture (21.8 per cent). In patients whose specimens were in the other three groups, sputum "conversion" was more than twice as frequent as in the first group (50, 55, and 45.4 per cent). In general, in patients whose sputum on admission was positive for tubercle bacilli both on microscopy and culture, the resected specimen was likewise

TABLE 4*A*

SUMMARY: RELATIONSHIP OF THE BACTERIOLOGIC FINDING OF TUBERCLE BACILLI IN THE SPECIMEN TO THE ADMISSION AND PREOPERATIVE SPUTUM FINDINGS

Bacteriology of Resected Specimen	Total Number of Patients	Per Cent	Number of Patients with Positive Sputum Culture on Admission	Per Cent	Number of Patients with Preoperative Positive Sputum	Per Cent	Number of Patients with Sputum Conversion	Per Cent
Positive microscopy; positive culture	46	100	41	89.2	31	67.4	10	21.8
Negative microscopy; positive culture	6	100	6	100	3	50.0	3	50.0
Positive microscopy; negative culture	18	100	15	83.3	5	27.8	10	55.5
Negative microscopy; negative culture	11	100	6	54.5	1	9.1	5	45.4
Totals	81	100	68	84.0	40	49.4	28	34.6

positive both on microscopy and culture; when the admission sputum was negative on microscopy and culture, the resected specimen was most often negative. This indicates that the sputum findings before chemotherapy furnish a good forecast of the viability of the bacilli eventually to be found in the resected specimen.

TABLE 4*B*

RELATIONSHIP OF THE BACTERIOLOGIC FINDING OF TUBERCLE BACILLI IN THE SPECIMEN TO THE ADMISSION AND PREOPERATIVE SPUTUM FINDINGS

Preoperative Sputum	Bacteriology of Specimen												
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Positive microscopy; positive culture	14	11	78.6	1	7.1	12	85.7	2	14.3	0	0	2	14.3
Negative microscopy; positive culture	26	20	76.9	2	7.7	22	84.6	3	11.5	1	3.9	4	15.4
Positive microscopy; negative culture	1	1	100.0	0	0	1	100.0	0	0	0	0	0	0
Negative microscopy; negative culture	40	14	35.0	3	7.5	17	42.5	13	32.5	10	25.0	23	57.5
Total	81	46	56.8	6	7.4	52	64.2	18	22.2	11	13.6	29	35.8

TABLE 5

GROWTH PERIODS OF CULTURES OF TUBERCLE BACILLI ISOLATED FROM THE RESECTED LESIONS

Type of Lesion	Period in Weeks															
	2	3	4	Per Cent with Growth after 4 Weeks	5	6	7	8	9	10	11	12	13	14	15	16	Total
Cavernous																	
Small size	0	3	8	60.0	0	1	5	0	1	0	0	0	0	0	0	1	19
Medium size	3	7	11	60.0	3	3	3	5	0	3	0	0	0	0	0	0	38
Large size	10	1	6	53.0	7	3	0	2	1	0	1	0	1	0	0	0	32
All sizes	13	11	25	55.0	10	7	8	7	2	3	1	0	1	0	0	1	89
Closed caseous																	
Small size	2	7	17	53.0	2	3	4	3	0	0	1	6	2	0	0	2	49
Medium size	0	5	8	50.0	7	0	0	1	0	0	3	2	0	0	0	0	26
Large size	2	3	4	60.0	1	2	0	0	0	1	1	1	0	0	0	0	15
All sizes	4	15	29	53.0	10	5	4	4	0	1	5	9	2	0	0	2	90
Total	17	26	54	54.0	20	12	12	11	2	4	6	9	3	0	0	3	179

Slightly more than one-third of all patients had preoperative sputum "conversion" (34.6 per cent), but in 35.7 per cent of these, some lesion or lesions from the resected specimen yielded positive results on both microscopy and culture. The interest of the findings recorded in table 4*B* lies not so much in the high coincidence of positive findings in both sputum and specimen as in the high percentage of positive findings (42.5 per cent) in specimens resected from "sputum-negative" patients. This again points to the large number of closed lesions which harbor viable organisms and throws doubt on the validity of "negative" preoperative sputum findings as the expression of an over-all effect of chemotherapy.

TABLE 6

RELATIONSHIP OF CAVERNOUS AND CLOSED CASEOUS LESIONS IN THE SAME SPECIMEN

Bacteriology of Cavernous Lesions	Total Number	Bacteriologic Finding of Tubercle Bacilli in Closed Caseous Lesions											
		Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Positive microscopy; positive culture	33	22	66.7	4	12.1	26	78.8	5	15.1	2	6.1	7	21.2
Negative microscopy; positive culture	4	3	75.0	1	25.0	4	100.0	0	0	0	0	0	0
Total	37	25	67.6	5	13.5	30	81.1	5	13.5	2	5.4	7	18.9
Positive microscopy; negative culture	12	1	8.3	0	0	1	8.3	8	66.7	3	25.0	11	91.7
Negative microscopy; negative culture	7	0	0	1	14.3	1	14.3	0	0	6	85.7	6	85.7
Total	19	1	5.3	1	5.3	2	10.6	8	42.1	9	47.3	17	89.4

TABLE 7*A*

RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Cavernous Lesions: Small Size											
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–6 months	9	0	0	1	11.1	1	11.1	0	0	8	88.9	8	88.9
7–12 months	27	6	22.2	4	14.8	10	37.0	11	40.8	6	22.2	17	63.0
13–18 months	11	3	27.3	0	0	3	27.3	3	27.3	5	45.4	8	72.7
More than 18 months	6	3	50.0	1	16.7	4	66.7	0	0	2	33.3	2	33.3
Total	53	12	22.7	6	11.3	18	34.0	14	26.4	21	39.6	35	66.0

The growth periods of the cultures of tubercle bacilli from lesions of all types and sizes are tabulated in table 5. The incubation period of the cultured material was twenty-six weeks, after which the tubes were discarded. No cultures became positive for tubercle bacilli after sixteen weeks of incubation. Larson and associates (6) similarly failed to obtain growth after the same period from lesions of isoniazid-treated patients. In the great majority of specimens which were positive during that period, growth was obtained in 54 per cent of the specimens within four weeks and in 85 per cent within eight weeks. The small closed caseous nodule here again commands special interest. From 53 per cent of such lesions tubercle bacilli grew within four weeks, again signifying the viability of organisms in these smallest tuberculous units. There was no appreciable difference in growth patterns between open and closed lesions (55 against 53 per cent) or between the various sizes of lesions in the two categories.

The bacteriologic comparison of "open" lesions with closed "satellite" lesions obtained from the same specimen, as set forth in table 6, raises points of extreme

TABLE 7*B*

RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Cavernous Lesions: Medium Size											
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–6 months	12	2	16.7	1	8.3	3	25.0	2	16.7	7	58.3	9	75.0
7–12 months	19	11	57.9	1	5.3	12	63.2	2	10.5	5	26.3	7	36.8
13–18 months	16	9	56.2	1	6.3	10	62.5	4	25.0	2	12.5	6	37.5
More than 18 months	15	9	60.0	1	6.7	10	66.7	3	20.0	2	13.3	5	33.3
Total	62	31	50.0	4	6.5	35	56.5	11	17.7	16	25.8	27	43.5

TABLE 7*C*

RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Cavernous Lesions: Large Size											
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–6 months	0	0	0	0	0	0	0	0	0	0	0	0	0
7–12 months	19	10	52.6	0	0	10	52.6	7	36.8	2	10.6	9	47.4
13–18 months	7	3	42.9	4	57.1	7	100.0	0	0	0	0	0	0
More than 18 months	19	12	66.7	2	5.5	14	72.2	2	11.1	3	16.7	5	27.8
Total	45	25	55.6	6	13.3	31	68.9	9	20.0	5	11.1	14	31.1

TABLE 7D

RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Closed Caseous Lesions: Small Size											
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–6 months	15	1	6.7	5	33.3	6	40.0	0	0	9	60.0	9	60.0
7–12 months	52	7	13.5	6	11.5	13	25.0	14	27.0	25	48.0	39	75.0
13–18 months	14	2	14.3	2	14.3	4	28.6	3	21.4	7	50.0	10	71.4
More than 18 months	45	14	31.1	10	22.2	24	53.3	11	24.5	10	22.2	21	46.7
Total	126	24	19.0	23	18.3	47	37.3	28	22.2	51	40.5	79	62.7

TABLE 7E

RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Closed Caseous Lesions: Medium Size											
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–6 months	7	0	0	0	0	0	0	2	28.6	5	71.4	7	100.0
7–12 months	23	4	17.4	3	13.0	7	30.4	9	39.2	7	30.4	16	69.6
13–18 months	26	9	34.6	6	23.1	15	57.7	6	23.1	5	19.2	11	42.3
More than 18 months	19	3	15.8	2	10.6	5	26.4	7	36.8	7	36.8	14	73.6
Total	75	16	21.4	11	14.6	27	36.0	24	32.0	24	32.0	48	64.0

TABLE 7F

RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Closed Caseous Lesions: Large Size											
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–6 months	7	1	14.3	0	0	1	14.3	0	0	6	85.7	6	85.7
7–12 months	12	5	41.7	0	0	5	41.7	5	41.7	2	16.6	7	58.3
13–18 months	1	0	0	1	100.0	1	100.0	0	0	0	0	0	0
More than 18 months	19	8	42.1	1	5.3	9	47.4	5	26.3	5	26.3	10	52.6
Total	39	14	35.9	2	5.2	16	41.1	10	25.6	13	33.3	23	58.9

TABLE 7G

SUMMARY: RELATIONSHIP OF DURATION OF CHEMOTHERAPY, TYPE OF LESION, AND BACTERIOLOGIC FINDING OF TUBERCLE BACILLI

Duration of Chemotherapy	Cavernous Lesions												Closed Caseous Lesions												Total Number of Lesions
	Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures		Total Number	Positive Microscopy Positive Culture		Negative Microscopy Positive Culture		Total Number of Positive Cultures		Positive Microscopy Negative Culture		Negative Microscopy Negative Culture		Total Number of Negative Cultures		
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	
0–6 months.....	21	2	9.5	2	9.5	4	19.0	2	9.5	15	71.5	17	81.0	29	2	6.9	5	17.2	7	24.1	2	6.9	20	69.0	22	75.9	50
7–12 months....	65	27	41.5	5	7.7	32	49.2	20	30.8	13	20.0	33	50.8	87	16	18.4	9	10.3	25	28.7	28	32.2	34	39.1	62	71.3	152
13–18 months.....	34	15	44.1	5	14.7	20	58.8	7	20.6	7	20.6	14	41.2	41	11	26.9	9	21.9	20	48.8	9	21.9	12	29.3	21	51.2	75
More than 18 months.....	40	24	60.0	4	10.0	28	70.0	5	12.5	7	17.5	12	30.0	83	25	30.1	13	15.7	38	45.8	23	27.7	22	26.5	45	54.2	123
Total.....	160	68	42.5	16	10.0	84	52.5	34	21.3	42	26.2	76	47.5	240	54	22.5	36	15.0	90	37.5	62	25.8	88	36.7	150	62.5	400

interest. Indeed, these results are considered to represent the most important feature of the study. When the cavernous lesion yielded tubercle bacilli on culture, 81.01 per cent of the satellite lesions, most of them of small size, likewise yielded positive cultures. When the cavity contents were negative for tubercle bacilli, only 10.6 per cent of the closed lesions were positive. This suggests that the difference in the behavior of organisms in necrotic or partially necrotic lesions in the same individual are minor, if indeed they exist at all. These results strongly suggest that the same forces are at work on the microorganism in all lesions regardless of their size, of the presence or absence of bronchial communication, and of differences in perifocal encasement.

The six tables (7*A* through *F*) deal with the effect of the duration of chemotherapy on the various types of resected lesion. In open cavities of all sizes, prolonged chemotherapy not only failed to effect bacterial death in their contents, but there was a higher percentage of positive results after six months of therapy. The chief cause of this was probably the emergence of drug-resistant tubercle bacilli and the resurgence of growth after the initial inhibition of metabolic activity. To some extent, however, the figures were influenced by the tendency to delay the operation and to prolong the period of preoperative chemotherapy for cavities which had failed to respond roentgenographically and bacteriologically during the early months of treatment. The larger the cavity, the longer was the duration of preoperative chemotherapy. This period was extended to at least one year in 57.7 per cent of the large, in 50 per cent of the medium-sized, and in 32 per cent of the small cavities. In all cavities considered as a single group, the chemotherapy had been continued for at least one year in 46.2 per cent. In closed caseous lesions, the increase in cultures positive for tubercle bacilli was seen after twelve months. The summarized results in table 7*G* for the total number of open and closed lesions regardless of size show a steady increase of cultures positive for tubercle bacilli from specimens with longer duration of chemotherapy. The results suggest that the optimal period for surgical resection lies within the first six months of chemotherapy, certainly within the first year. In general, this recommendation coincides with that of Hughes (7), although he based his conclusions on different bacteriologic findings.

Discussion

One of the facts which has emerged from the investigations of recent years is the occurrence of caseation in tuberculous lesions at an earlier stage than used to be believed by pathologists of previous generations. Medlar (8) found caseation in all minimal infiltrates. Even lesions of very small size, which apparently had developed without the confluence of a multiplicity of tubercles, showed caseation in the present study. This suggests that the majority of all foci have necrotic centers. Canetti (2) has pointed out that caseous lesions are relatively refractory to chemotherapy, and the present findings of the comparatively high bacillary activity of the small lesions after treatment substantiate this contention. Dubos (9) has explained the failure of caseous lesions to respond to chemotherapy as the result of "broken down tissue components of unknown chemical composition, many of which are likely to act as direct inhibitors."

It seems that the difference between the behavior of tubercle bacilli in cavities and in even the smallest closed lesions is not nearly as great as was assumed in the past.

For the clinician, these findings need not be any cause for pessimism, but should serve as a warning that the potentialities for drug therapy of tuberculosis are more limited than they might have appeared to be during the earlier period. The open cavity as a reservoir of accumulated tubercle bacilli and as the chief distributor of future infection should be removed surgically whenever possible if it fails to close under medical therapy of several months' duration. It has been the experience of the present writers that cavities which have not closed under drug therapy after six months are not likely to do so under more prolonged treatment. The therapeutic aim should be to resect the cavity when it has become an isolated residual, i.e., after the noncavernous tuberculous involvement has been subdued and eliminated as a major source of future re-exacerbation. The high incidence of persisting viable tubercle bacilli in a large percentage of even the smallest satellite lesions threatens to reduce the over-all lasting effectiveness of resectional surgery after it has reduced bronchogenic redistribution to the attainable minimum. However, this should not be considered as a cause for extending resections to preoperatively unconsidered parts of the lung when granular lesions can be palpated during operation. Confluence of such lesions which leads to new more massive involvement and new excavation may never occur and, for the sake of the respiratory capacity, it must be accepted as a calculated risk to leave them *in situ*. For the maximal attainable safety, prolonged chemotherapy as proposed by Dooneief and Hite (10) is indicated in spite of the emergence of drug-resistant tubercle bacilli and the possibility of resurgence of viability.

As yet the study of smaller closed caseous foci has been too scant to pass judgment on their ultimate fate with or without long-term chemotherapy. Until more reliable information is available, it would be an unnecessary gamble to discontinue prematurely chemotherapy which can be assumed to restrain the viability of the bacterial content of the lesion, although it will not subdue it completely in many cases.

Clinical experience has shown that, although increasing resistance interferes with the effect of the drugs on bacillary activity, nevertheless clinical results are sustained and improved under prolonged chemotherapy. Almost all of the writers' patients who returned with reactivated disease after discharge from the hospital admitted that they had discontinued chemotherapy of their own volition.

Undoubtedly the greatest advance in chemotherapy would be the arrival of more drugs as unquestioned in their specific competence as streptomycin and isoniazid; they would allow for a new therapeutic attack when the effect of previously used drugs has weakened with the development of increasing bacillary resistance. This alone could bring chemotherapy to a peak of effectiveness.

Summary

Four hundred open and closed tuberculous lesions of all sizes obtained by resectional surgery from 81 patients were studied bacteriologically, both by direct microscopic examination and by culture. The essential results were those obtained by culture.

The majority of all lesions, even of the small closed ones, were found to contain caseous material. The small closed foci which constituted nearly one-third of the entire material were considered a feature of special interest. Whether a cavity contained tubercle bacilli depended to some extent upon its size, the largest ones yielding the greatest number of "positive" cultures. In the closed lesions, size was of no significant influence.

Slightly more than one-third of all patients had preoperative sputum "conversion," but in 35.7 per cent of them one or more lesions in the resected specimen were positive for tubercle bacilli on microscopy and culture. The percentage of patients with preoperative sputum "conversion" was smallest in the group in which the specimen was "positive" both on microscopy and culture. The status of the sputum with respect to tubercle bacilli before the beginning of chemotherapy furnishes a good forecast of bacteriologic findings in the specimen.

From the majority of culturally positive lesions, growth of tubercle bacilli was obtained within four weeks. The type and size of the lesions had no influence on the rapidity of growth. The cultural results from closed foci conformed closely to those from open cavities in the same specimen. Cavities from which tubercle bacilli were cultured coexisted with 81.1 per cent of culture-"positive" closed lesions; cavities from which tubercle bacilli were not cultured coexisted with only 10.6 per cent of culture-"positive" closed lesions.

The duration of preoperative chemotherapy had a great influence on the cultural response of resected lesions. In both open cavities and closed foci, progressive bacterial resistance under prolonged treatment resulted in a greater number of cultures from the specimen which were positive for tubercle bacilli. The crucial period seems to lie between six and twelve months.

Sumario

La Bacteriología de las Lesiones Tuberculosas Resecadas después de la Quimioterapia

Cuatrocientas lesiones tuberculosas abiertas y cerradas de diversos tamaños, obtenidas por la resección quirúrgica de 81 enfermos, fueron estudiadas bacteriológicamente, tanto por el examen microscópico directo como por cultivo. Los resultados esenciales fueron los obtenidos con el cultivo.

En la gran mayoría de las lesiones, aun en las pequeñas y cerradas, se observó que contenían materias caseosas. Los pequeños focos cerrados que constituían casi la tercera parte de todo el material se consideraron como punto de interés destacado. La existencia de bacilos tuberculosos en una caverna dependió hasta cierto punto del tamaño de ésta, rindiendo las cavernas más grandes el mayor número de cultivos "positivos." En las lesiones cerradas, el tamaño no ejerció influjo significativo.

En poco más de una tercera parte de los enfermos hubo "viraje" preoperatorio del esputo, pero en 35.7 por ciento de ellos una o más lesiones del ejemplar resecado fueron positivas para bacilos tuberculosos en frotes y en cultivos. El porcentaje de enfermos con "viraje" preoperatorio del esputo alcanzó su mínimo en el grupo en el que el ejemplar resultó "posi-

tivo" tanto en frote como en cultivo. La clasificación del esputo con respecto a bacilos tuberculosos antes de empezar la quimioterapia facilita una buena predicción de los hallazgos bacteriológicos en el ejemplar.

De la mayoría de las lesiones "positivas" culturalmente, se obtuvieron colonias de bacilos tuberculosos en término de cuatro semanas. La clase y el tamaño de las lesiones no afectaron la rapidez de la proliferación. Los resultados de los cultivos de los focos cerrados se aproximaron sumamente a los de las cavernas abiertas en el mismo ejemplar. Con las lesiones cerradas de cultivos "positivos" coexistieron en 81.1 por ciento de los casos cavernas de las que se cultivaron bacilos tuberculosos y sólo en 10.6 por ciento cavernas de las que no se cultivaron tales bacilos.

La duración de la quimioetrapa preoperatoria ejerció un gran influjo sobre la respuesta cultural de las lesiones resecadas. Tanto en las cavernas abiertas como en los focos cerrados, la progresiva resistencia bacteriana bajo tratamiento prolongado dió por resultado un número mayor de cultivos del ejemplar que eran positivos para bacilos tuberculosos. El período crítico parece quedar entre seis y doce meses.

Resume

Bactériologie des lésions tuberculeuses réséquées après chimiothérapie

Une étude bactériologique de 400 lésions tuberculeuses ouvertes ou oblitérées et de dimensions variées, obtenues par résection chirurgicale, a été effectuée à la fois par l'examen direct et par la culture. Les résultats essentiels sont ceux fournis par la culture.

La grande majorité de l'ensemble des lésions, même les plus petits foyers oblitérés, renfermaient des substances caséeuses. Les petits foyers oblitérés, qui constituaient près d'un tiers des pièces sont considérés comme des lésions offrant un intérêt particulier. La présence d'un nombre important de bacilles dans l'excavation dépendait, dans une certaine mesure, de ses dimensions, les plus grandes fournissant le plus grand nombre de cultures "positives". En ce qui concerne les lésions fermées, le facteur dimension était sans influence significative.

Un peu plus d'un tiers de la totalité des malades était devenu abacillifère avant l'intervention, mais chez 35,7% d'entre eux, les spécimens prélevés à partir d'une ou de plusieurs des lésions réséquées ont été trouvés "positifs" à l'examen direct et en culture. Le pourcentage des cas abacillifères avant l'intervention chirurgicale était le plus faible dans le groupe ou les spécimens étaient "positifs" à l'examen direct et en culture. En ce qui concerne le bacille tuberculeux, l'état de l'expectoration avant l'instauration de la chimiothérapie est un élément qui permet assez bien de prévoir les résultats de l'examen bactériologique de ces spécimens.

La culture de la majorité des lésions "positives" permettait d'obtenir des colonies de bacilles en quatre semaines. Le type et les dimensions des lésions étaient sans influence sur la rapidité de la croissance. Les résultats culturaux, en relation avec les foyers fermés, concordaient avec ceux obtenus avec la caverne ouverte du même spécimen. Le pourcentage de coexistence de lésions cavitaires, à partir desquelles les bacilles tuberculeux étaient recouvrés en culture, et de lesions fermées donnant des cultures "positives" atteignait 81,1% et le pourcentage de coexistence d'excavations, à partir desquelles les cultures étaient "négatives" et de lésions fermées donnant des cultures positives n'était que de 10,6%.

La durée de la chimiothérapie pré-opératoire exerçait une grande influence sur la réaction culturale des lésions réséquées. La résistance bactérienne progressive, qui se manifestait dans les cures prolongées a produit un plus grand nombre de cultures "positives" à partir des spécimens, qu'ils proviennent de cavernes ouvertes ou de foyers oblitérés. La période cruciale semble se trouver entre six et dix mois.

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PNEUMONECTOMY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1, 2, 3]

The Influence of Preoperative Clinical Findings upon the Early and Late Results

WALTER T. MILLER AND C. J. MARTIN

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INTRODUCTION

Between January 1, 1946, and June 30, 1955, 204 pneumonectomies were performed on tuberculous patients at Firland Sanatorium, Seattle. In January, 1956, a follow-up study of all of these patients was completed. In the present paper, the effects of preoperative clinical findings on early and late results are reported, the status of the patients having been classified as dead, alive but with relapse of disease, alive with restricted activity, or alive and well.

METHODS

The decision to operate on these patients was reached at therapy conferences. The pneumonectomies were performed by three thoracic surgeons or by a surgical resident under their supervision.

Details of the preoperative clinical findings and the operative and postoperative sanatorium course were obtained from the inpatient charts. The condition of discharged patients was ascertained by sending questionnaires to the agency or physician through whom the patient was being followed. Death certificates and autopsy reports were obtained on those who died after discharge.

The causes of death have been classified as (*1*) progressive tuberculosis, (*2*) tuberculosis and the pneumonectomy (included here are the cases in which direct or indirect effects of the surgery seemed to be the immediate cause of death), and (*3*) others or miscellaneous, i.e., any cause not falling into the first two categories.

The National Tuberculosis Association classification has been used to define the extent and the activity or inactivity of the disease. Relapse has been defined as roentgenographic evidence of reactivation of tuberculosis, bacteriologic proof of activity, or both, in patients who, according to National Tuberculosis Association standards, had inactive disease. In the evaluation of the preoperative clinical factors which might have contributed to the relapse, only the first relapse of the disease in patients who had shown reactivation more than once has been considered since it was believed that preoperative findings could be influential only once in each case. The chi-square test (1) was used to determine the statistical significance of preoperative clinical factors which might have influenced the effectiveness of the pneumonectomy.

RESULTS

Since the most recent operations included in this series were performed in June, 1955, the minimal follow-up period for patients alive in January, 1956, was

[1] From Firland Sanatorium, Seattle, Washington; and the Department of Medicine, University of Washington, School of Medicine, Seattle, Washington.

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[3] Presented before the medical session, as part of *Section 3A*, at the annual meeting of the National Tuberculosis Association, Kansas City, Missouri, May 7, 1957.

six months, the maximal being nine years. The following list shows the status of the patients in January, 1956.

Total number	204
Dead	53 (26%)
Lost	18 (9%)
Active disease	1 (0.5%)
Inactive disease	132 (64%)

Indications for surgery: In table 1 are shown the indications for the pneumonectomies, as laid down by the therapy conference. The largest category is extensive disease (71 cases), which includes complete destruction or widespread caseous or cavitary lesions of one lung. In the 40 cases of pneumonectomy following thoracoplasty failure, the majority of the failures were evidenced by bacteriologic relapse. In half of this group (20 cases), there was significant bronchial disease, which was presumed to have been a factor in the failure of the thoracoplasty. When the main indication was bronchial disease (20 cases), the disease was considered too extensive for a plastic procedure or was accompanied by sufficient parenchymal disease to warrant pneumonectomy. Nine cases were listed as "desperate risks." Such patients, treated in the era preceding long-term drug therapy, had progressive tuberculous pneumonia involving, principally, one lung.

It is of interest that 42 patients, one-fifth of the series, had pneumonectomies when the therapy conference had voted for a resection of lesser extent. In 33 (79 per cent) of these cases, pneumonectomies were performed because of technical difficulties at the time of surgery. In 9 cases the surgeon elected to complete pneumonectomy because the disease was more extensive than had been suspected preoperatively.

Deaths: Of the 204 patients in this series, 53 (26 per cent) are known to be dead. The causes of death are listed under the three main headings in table 2.

TABLE 1

INDICATIONS FOR PNEUMONECTOMY

(204 Cases)

Indication	Number of Cases	Dead*	Relapse	Activity Restricted
Extensive disease	71 (35%)	10	10	4
Thoracoplasty failure	40 (20%)	6	11	1
Bronchial disease	20 (10%)	2	2	1
Bronchopleural fistula	16 (8%)	8	3	1
"Desperate risk"	9 (4%)	5	1	0
Empyema	5 (2%)	1	2	1
Less than pneumonectomy decided on at therapy conference	42 (20.5%)	9	10	7
Other	1 (0.5%)	0	0	0
Total	204 (100%)	41	39	15

* 12 deaths from miscellaneous causes not included.

TABLE 2

CAUSES OF DEATH FOLLOWING PNEUMONECTOMY
(204 Cases)

Progressive Tuberculosis		Tuberculosis with Pneumonectomy		Miscellaneous	
Progressive tuberculosis	13	Respiratory insufficiency	9	Myocardial infarction	2
		Cor pulmonale and right heart failure	7	Accident	2
		Bronchopleural fistula	5	Pulmonary embolus	1
		Shock	3	Cerebral thrombosis	1
		Cardiac arrest	1	Hypertension	1
		Mediastinal emphysema	1	Cardiac arrhythmia	1
		Cardiac arrhythmia	1	Heart failure	1
		Hemorrhage	1	Diabetes	1
				Suicide	1
				Unknown	1
Totals	13		28		12

Forty-one patients died from progression of their tuberculosis following surgery (13 cases) or from causes related to the removal of the lung (28 cases). The remaining 12 patients died from a variety of causes unrelated to either tuberculosis or the operation. These 12 deaths have not been included in the mortality rates given in tables 1 and 4.

The entire series of operations may be broken down into three smaller series: those performed from 1946 to 1948, in the pre-drug era; those from 1949 to 1951, the era of minimal preoperative chemotherapy; and those from 1952 to 1955, in the present era of "adequate" preoperative chemotherapy. The distribution of the cases and the summary of the operative deaths (within twenty-four hours) and early postoperative deaths (within thirty days after operation) in these three periods are given in table 3.

The operative mortality for the entire series was 2.5 per cent, and the mortality in the early postoperative period, 5.0 per cent. The 15 patients who died in these two periods were 7.5 per cent of the total series. Despite the improvement in preoperative therapy, the percentage of early postoperative deaths in 1952–1955 was practically the same as that in 1949–1951. On the other hand, pneumonectomy was considered necessary for only a third as many patients in the later period.

In the late postoperative period, 11 patients (5 per cent of the series) died of progressive tuberculosis and 15 (7.5 per cent of the series) died of causes related to pneumonectomy. In relation to the era of operation, these deaths are distributed as follows. Among 22 patients in the 1946–1948 series who survived to the late postoperative period, there were no deaths from tuberculosis and only one death (0.5 per cent) from the effects of the pneumonectomy. Among 126 patients in the 1949–1951 series, 8 deaths (6 per cent) from tuberculosis and 12 deaths (9 per cent) from pneumonectomy occurred; and among 41 patients in the

TABLE 3

SUMMARY OF OPERATIVE AND EARLY POSTOPERATIVE DEATHS

25 cases	*1946–1948*	
	1 operative death	Cardiac arrest
	2 early postoperative deaths	Progressive tuberculosis
		Respiratory insufficiency
135 cases	*1949–1951*	
	3 operative deaths	Pulmonary hemorrhage
		Shock
		Respiratory insufficiency
	6 early postoperative deaths	Bronchopleural fistula
		Cardiac arrhythmia
		Mediastinal emphysema
		Shock
		Respiratory insufficiency
		Progressive tuberculosis
44 cases	*1952–1955*	
	1 operative death	Shock
	2 early postoperative deaths	Respiratory insufficiency

1952–1955 series, 3 deaths (7 per cent) from tuberculosis and 3 deaths (7 per cent) from pneumonectomy occurred.

Relation of Preoperative Findings to Deaths

Indications for surgery: When patients were grouped according to the main indications for surgery (*see* table 1), the mortality rates from progression of tuberculosis appeared significantly high among the "desperate risk" (55 per cent mortality, $P = 0.001$) and, questionably, the bronchopleural fistula (50 per cent mortality, $P = 0.05$) groups. Deaths from causes related to pneumonectomy were not significantly related to any indication for surgery ($P > 0.10$).

Age: After exclusion of deaths from unrelated causes, the mortality rate among the patients more than forty years old was higher than that among those less than forty years (table 4). Progression of tuberculosis caused the death of 5 patients (7 per cent) more than forty and of 8 (6 per cent) less than forty years old. This difference is obviously insignificant. Deaths related to pneumonectomy occurred in 16 patients (21 per cent) more than forty and 12 (9 per cent) less than forty ($P = 0.03$) (table 4). Three patients less than forty and 9 more than forty died of causes unrelated to tuberculosis or pneumonectomy.

Sex: Nine males (8 per cent) and 4 females (4 per cent) died from progression of their tuberculosis ($P > 0.10$); 21 males (19 per cent) and 7 females (7 per cent) died of causes related to pneumonectomy ($P = 0.03$) (table 4). (Of the deaths from unrelated causes, 7 occurred among the men and 5 among the women.)

The correlation of death related to pneumonectomy with sex and age may be somewhat misleading since the cases in this series were not evenly divided according to age and sex. The incidence of far advanced tuberculosis was not

TABLE 4

PREOPERATIVE CLINICAL FINDINGS AND RESULT OF PNEUMONECTOMY
(204 Cases)

Factors Studied	Total Cases	Dead*	Relapses	Restricted Activity
Age				
<40	128 (63%)	20 (15%)	24 (19%)	8 (6%)
>40	76 (37%)	21 (28%)	15 (20%)	7 (9%)
Sex				
Male	110 (54%)	30 (27%)	26 (24%)	13 (12%)
Female	94 (46%)	11 (11%)	13 (14%)	2 (2%)
Race				
White	163 (80%)	35 (21%)	32 (20%)	12 (7%)
Negro	18 (9%)	3 (17%)	4 (22%)	1 (6%)
Oriental	10 (5%)	1 (10%)	2 (20%)	0
Other	13 (6%)	2 (15%)	1 (8%)	2 (15%)
Side				
Right	82 (40%)	17 (21%)	19 (23%)	5 (6%)
Left	122 (60%)	24 (19%)	20 (16%)	10 (8%)
Classification of disease (on admission)				
Far advanced	178 (88%)	39 (22%)	34 (19%)	12 (7%)
Moderately advanced	23 (11%)	2 (9%)	5 (22%)	3 (13%)
Minimal	3 (1%)	0	0	0
Classification of disease (unoperated lung on admission)				
Far advanced	10 (5%)	5 (50%)	2 (20%)	3 (30%)
Moderately advanced	70 (34%)	21 (30%)	12 (17%)	2 (3%)
Minimal or none	124 (61%)	15 (12%)	25 (20%)	10 (8%)
Preoperative drugs				
None	27 (13%)	6 (22%)	8 (29%)	3 (11%)
<1 month	52 (26%)	10 (19%)	7 (13%)	3 (6%)
1–6 months	94 (46%)	20 (21%)	21 (22%)	6 (6%)
>6 months	31 (15%)	5 (16%)	3 (9%)	3 (9%)
Endobronchitis				
+	53 (26%)	15 (28%)	11 (21%)	3 (6%)
−	138 (68%)	21 (15%)	26 (12%)	12 (9%)
Not known	13 (6%)	5 (39%)	2 (15%)	0
Preoperative sputum status				
Positive for *M. tuberculosis* <1 month preoperatively	61 (30%)	16 (26%)	18 (29%)	3 (5%)
Positive for *M. tuberculosis* >1 month preoperatively	126 (62%)	22 (17%)	20 (16%)	9 (7%)
Negative	8 (4%)	1 (12%)	1 (12%)	3 (37%)
Not known	9 (4%)	2 (22%)	0	0
Preoperative temporary collapse				
Pneumoperitoneum	55 (27%)	8 (15%)	13 (24%)	4 (7%)
Pneumothorax	45 (22%)	8 (18%)	9 (20%)	3 (7%)
None	104 (51%)	25 (24%)	17 (16%)	8 (8%)

* Dead excludes 12 deaths not due to tuberculosis or pneumonectomy.

significantly greater in males than females, but the men as a group were significantly older. Only 45 per cent of the patients less than forty years old were males; while 65 per cent of the patients more than forty were males ($P < 0.02$).

Race: The death rates from progression of the disease or from surgery among the various racial groups (table 4) were not significantly different.

Side of operation: Although the mortality rate following removal of the right lung (21 per cent) was slightly higher than that following removal of the left lung (19 per cent) (table 4), this difference is statistically insignificant.

Extent of disease (table 4): As would be expected, the patients with the most advanced disease at the time of admission were most frequently victims of progression of their tuberculosis ($P < 0.01$), but the extent of disease was not a factor in the incidence of death from pneumonectomy ($P > 0.10$).

Disease in the unoperated lung: The extent of tuberculosis in the unoperated lung at the time of admission to the hospital (table 4) was determined from the roentgenogram. The state of the unoperated lung was the one significant factor common to death from progression of the tuberculosis ($P < 0.001$) and death from causes related to the pneumonectomy ($P < 0.01$).

Preoperative drug therapy: As shown in table 4, the cases were divided into four groups according to the duration of preoperative chemotherapy. The death rates related to tuberculosis and/or surgery were not significantly affected by the length of time the drugs had been administered, nor even by complete absence of preoperative drug therapy.

Endobronchitis: In 13 cases, no preoperative bronchoscopy was done. The bronchoscopist diagnosed tuberculous endobronchitis in 32 patients and nonspecific endobronchitis in 21. No inflammation was noted in the other 138 patients. One of the 32 patients with tuberculous endobronchitis died of progressive tuberculosis and 4 died of causes related to the pneumonectomy. Of the 21 with nonspecific endobronchitis, 2 died of progression of tuberculosis and 8 from causes related to the operation. The preoperative bronchoscopic findings were not significantly related to the death rate from tuberculosis, but were a significant factor in the incidence of death allied to the pneumonectomy ($P < 0.01$). Particularly significant ($P < 0.005$) was the nonspecific endobronchitis, which was described as edema and inflammation at the time of visualization.

Preoperative sputum status: Microscopy or culture of a three-day specimen was used to determine the presence of tubercle bacilli in the sputum. When the patients were grouped according to this preoperative factor (table 4), no significant difference was observed.

Temporary collapse: Treatment with a pneumoperitoneum or a pneumothorax prior to the pneumonectomy did not prove to be a factor in the incidence of death.

To sum up: The significant predisposing factors in death from progressive tuberculosis were: (*1*) "desperate risk" ($P = 0.001$) or, possibly, bronchopleural fistula ($P = 0.05$) as an indication for surgery; (*2*) the extent of tuberculosis on admission; and (*3*) the extent of disease in the unoperated lung on admission ($P < 0.001$). All other preoperative factors evaluated were not statistically related to deaths from this cause.

Deaths from causes related to pneumonectomy for tuberculosis were significantly correlated with: age ($P = 0.03$), sex ($P = 0.03$), extent of disease in the unoperated lung on admission to the hospital ($P < 0.01$), and preoperative bronchoscopic findings ($P < 0.01$). The other factors examined were not significant in this context.

Preoperative Clinical Findings and Subsequent Relapse

The disease of 39 patients (19 per cent) relapsed one or more times during the follow-up period. As stated earlier, only the first relapse is counted here since it is unlikely that preoperative factors would affect an individual more than once. Summarizing figures are to be found in tables 1 and 4.

None of the following factors was significantly related to the incidence of relapse: indications for surgery ($P > 0.50$), age ($P > 0.50$), sex ($P > 0.05$), race ($P > 0.50$), side of operation ($P > 0.50$), extent of disease on admission ($P > 0.50$), extent of disease in the unoperated lung on admission ($P = 0.50$), length of preoperative drug therapy ($P > 0.10$), preoperative bronchoscopic findings ($P > 0.50$), preoperative sputum status ($P > 0.50$), or preoperative temporary collapse ($P > 0.10$).

Preoperative Clinical Findings and Subsequent Restriction of Activity

The physicians and agencies engaged in the follow-up study at the end of 1955 were asked if the patient was leading a normal life or if his activity was moderately or severely restricted as a result of his disease and surgery. Of the 132 known to be alive with inactive disease, 117 (89 per cent) had no significant restriction; while 15 (11 per cent) had moderate or severe restriction (table 4). Only the following three factors among the preoperative clinical findings evaluated in this study were related to restriction of activity: sex, disease in the unoperated lung, and preoperative sputum status.

Sex: Thirteen (12 per cent) of 110 males and only 2 (2 per cent) of 94 females were under restricted physical activity. This result is statistically significant ($P = 0.005$).

Disease in the unoperated lung: Three of the patients whose postoperative activity was restricted had had far advanced disease in the unoperated lung at the time of admission, 2 had had moderately advanced disease, and 10 had had little or no disease in that lung. These figures are statistically significant ($P < 0.01$). The incidence of restricted activity was greatest in the group with far advanced disease at the time of admission ($P < 0.01$).

Preoperative sputum status: As a factor in the incidence of restricted activity, the presence or absence of tubercle bacilli in the sputum before operation approached significance ($P = 0.05$). The incidence of restricted physical activity was greatest among patients with sputum negative for *M. tuberculosis*. There is no explanation for this finding, but the small number of cases in this category makes this finding of doubtful value.

Discussion

The indications for removal of the entire lung in the treatment of tuberculosis were similar to those listed by others (2–5). Pneumonectomy for tuberculosis is often a last-ditch effort to convert a patient with advanced disease and in poor general condition from an infectious to a noninfectious state. When the charts of this series are reviewed, it is surprising to find how often this was achieved. An unexpectedly large percentage (16 per cent) of the pneumonectomies in this series were completed because technical difficulties arose during the operation. This occurrence is not emphasized in the literature.

The preponderance of left pneumonectomies would not seem to bear out the concept that pulmonary tuberculosis in the left lung is more easily controlled than that in the right (6). Others (7) have also reported a higher incidence of left pneumonectomies in the treatment of pulmonary tuberculosis. Contrary to the finding of Robinson and associates (3), subsequent death was not influenced by the side of operation in the present series.

It is interesting that race played no part in the incidence of death, relapse, or restriction of activity. It has been held that non-white groups have a poor tolerance for tuberculosis but, at least in treatment with pneumonectomy, this factor is not evident in this series.

The length of preoperative drug therapy did not prove to have an influence on the postoperative death rate. This factor was insignificant whether progression of tuberculosis or death as related to the pneumonectomy was considered. It should be remembered that those patients who received no chemotherapy, or very short courses of preoperative chemotherapy, were patients during the earlier years studied when the pneumonectomy was preceded by long periods of bed rest, supplemented in many instances by minor collapse procedures. The stability of the disease at the time of surgery may well have been equal to that in more recent, drug-treated patients. Overholt (8) has stated that there is no difference in the risk of operation or in the incidence of complications when patients receiving drug therapy for less than a month preoperatively are compared with those treated for longer periods. The present series showed no difference in the operative mortality or the rate of early postoperative deaths during the different eras of drug therapy. The incidence of late postoperative deaths, as well as of relapse and of restriction of activity, was unaffected by the duration of preoperative drug therapy.

Deaths from progressive tuberculosis would indicate that pneumonectomy was inadequate to handle the type of disease present. Such failures most frequently occurred in cases of advanced disease. The extent of disease in the unoperated lung was also significant. The one indication for surgery which was, without question, significantly related to death was extensive and fulminant disease, i.e., progressive tuberculous pneumonia which made the operation a "desperate risk." Thus, the three preoperative clinical findings which were significant in the incidence of death from progression of the tuberculosis were related to the preoperative type or extent of disease. Geake and Young (9) found that the extent of tuberculosis in the resected specimen had no appreciable influence upon the

prognosis, but that recent disease in the unoperated lung was a factor in postoperative deterioration. In the present series, no distinction was made between recent and long-standing disease in the contralateral lung.

Deaths from causes related to the pneumonectomy were divided into the operative, the early postoperative, and the late postoperative periods. The inclusion of cases in the last group was often based on arbitrary decisions. In the main, the patients included had respiratory insufficiency or cor pulmonale progressing from the date of operation. Deaths from causes related to the pneumonectomy were significantly higher in older patients and in males. The reasons for the preponderance of male deaths may be those stated by Davidson and coworkers (10): that the female more readily accepts surgery, the larger number of chronic alcoholics among males, and the older age in males. Males in the present series were significantly older and included a higher percentage of chronic alcoholics.

The most important preoperative bronchoscopic finding in the incidence of death was a nonspecific endobronchitis, the diagnosis being based on the discovery of inflammation and edema. All patients with this preoperative diagnosis were found to have tuberculous endobronchitis when the surgical specimen was examined by the pathologist. The effect of endobronchitis on the postoperative course of tuberculosis has been noted by others (11).

As might be expected, the extent of the disease in the unoperated lung was significant in the incidence of death from pneumonectomy. Pulmonary function studies were completed on the majority of these cases, and will be reported in another paper.

None of the 11 preoperative clinical factors studied affected the relapse rate.

Sixty-four per cent of the 204 patients in the series were alive with inactive disease at the end of the study, including 7 per cent with marked restriction of activity.

Summary

Two hundred and four pneumonectomies in the treatment of pulmonary tuberculosis were performed at Firland Sanatorium between January, 1946 and June, 1955. The indications for surgery were generally those listed by other writers, but 20 per cent of the patients in the present series had pneumonectomies when resection of lesser extent was scheduled. In the majority of such cases, technical difficulties during the operation necessitated the greater excision. The operative mortality (within twenty-four hours) of the series was 2.5 per cent, and a further 5 per cent died in the thirty days following surgery. In January, 1956, 53 of the 204 patients were dead from all causes; one was in the sanatorium; and 132 (64 per cent) had inactive disease. The condition of 18 former patients could not be learned.

On the basis of the present series, the preoperative clinical findings significantly affecting the incidence of death from progression of the tuberculosis were the extent of the disease on admission, the extent of the disease in the unoperated lung on admission, and certain indications for the operation. The "desperate

risk" patients and, possibly, those with preoperative bronchopleural fistulas did poorly.

Deaths from causes related to pneumonectomy for the disease were significantly more frequent among males and older patients. Again, the extent of the disease in the unoperated lung was a significant factor, as was the preoperative finding of inflammation and edema in the bronchi of the resected lung.

No preoperative clinical factor studied affected subsequent relapse. Subsequent restriction of physical activity following pneumonectomy was greater in male patients and in those with more extensive preoperative disease in the unoperated lung.

Sumario

La Neumonectomía en el Tratamiento de la Tuberculosis Pulmonar: El Influjo de los Hallazgos Clínicos Preoperatorios sobre los Resultados Tempranos y Tardíos

En el Sanatorio Firland ejecutaron entre enero de 1946 y junio de 1955 204 neumonectomías para tratamiento de la tuberculosis pulmonar. Las indicaciones para la cirugía fueron generalmente las citadas por otros autores, pero en 20 por ciento de los enfermos de la serie actual se hicieron neumonectomías aunque se había consignado una resección de menor alcance. En la mayoría de esos casos, dificultades técnicas surgidas durante la operación impusieron la excisión mayor. La mortalidad operatoria (en término de veinticuatro horas) en la serie fué de 2.5 por ciento y otro 5 por ciento falleció en los treinta días consecutivos a la cirugía. Para enero de 1956, 53 de los 204 enfermos habían fallecido de todas causas; uno estaba en el sanatorio; y 132 (64 por ciento) tenían enfermedad inactiva. No pudo averiguarse el estado de 18 de los antiguos enfermos.

A base de la serie actual, los hallazgos clínicos preoperatorios que afectan en forma importante la incidencia de la mortalidad debida a evolución de la tuberculosis son la extensión de la enfermedad al ingreso, la extensión de la enfermedad en el pulmón inoperado al ingreso y ciertas indicaciones para la operación. Los enfermos rotulados como "riesgos sin esperanza" y, posiblemente, los que tenían fístulas broncopleurales preoperatorias lo pasaron mal.

Las muertes debidas a causas relacionadas con la neumonectomía fueron notablemente más altas entre los varones y los enfermos más viejos. De nuevo, la extensión de la enfermedad en el pulmón inoperado fué un factor importante, como también lo fué el hallazgo preoperatorio de inflamación y edema en los bronquios del pulmón resecado.

Ningún factor clínico preoperatorio estudiado afectó las recidivas. La limitación subsiguiente de la actividad consecutivamente a la neumonectomía fué mayor en los varones y en los que tenían enfermedad preoperatoria más extensa en el pulmón inoperado.

Resume

La pneumonectomie dans le traitement de la tuberculose pulmonaire: Influence des signes cliniques pré-opératoires sur les résultats précoces et éloignés

Deux cent-quatre pneumonectomies furent pratiquées pour tuberculose pulmonaire au Firland Sanatorium entre Janvier 1946 et Juin 1955. Les indications du traitement chirurgical étaient en général celles signalées par d'autres auteurs, mais 20% des cas inclus dans la série actuelle avaient subi la pneumonectomie alors qu'une résection de moindre étendue avait été prévue. Dans la majorité des cas, l'excision plus importante était imputable à des difficultés techniques rencontrées au cours de l'intervention. La mortalité opératoire de cette série est de 2,5% et à laquelle s'ajoute une mortalité de 5% produite par les décès survenus dans le trente jours suivant l'opération. En janvier 1956, parmi les 204 malades, 53 avaient succombé à diverses causes; 1 malade était en sanatorium et la tuberculose était

stabilisée chez 132 malades (64%). Il n'a pas été possible de connaître l'état de 18 anciens malades.

D'après la série actuelle, les signes cliniques pré-opératoires affectant de façon significative l'incidence de la mort par progression de la tuberculose sont: l'étendue des lésions lors de l'admission à l'hôpital, l'étendue des lésions contro-latérales dans le poumon non opéré lors de l'admission, et certaines indications opératoires. Les cas considérés "in extremis" et, vraisemblablement, les cas où des fistules broncho-pleurales existaient avant l'opération ont donné de mauvais résultats.

Les décès dûs à des causes en relation avec la pneumonectomie pour tuberculose étaient plus fréquents parmi les sujets du sexe masculin et les vieillards. Il y a lieu d'insister sur l'importance presentée par l'étendue des lésions dans le poumon non-opéré et des signes pré-opératoires de réaction inflammatoire et oedémateuse dans les bronches du poumon réséqué.

Aucun des facteurs pré-opératoires ayant été étudié n'affectait la récidive ultérieure. La limitation de l'activité après pneumonectomie était plus grande chez les malades du sexe masculin et dans les cas où les lésions pré-opératoires du poumon non-opéré étaient les plus extensives.

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TUBERCULOUS PLEURISY WITH EFFUSION IN CHILDREN[1, 2]

A Study of 202 Children with Particular Reference to Prognosis

EDITH M. LINCOLN, PAMELA A. DAVIES, AND SOMCHAI BOVORNKITTI

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INTRODUCTION

Although many large series of patients with tuberculous pleurisy with effusion have been reported in adults, very few have dealt exclusively with pleurisy occurring in the pediatric age range. Only two writers have reported on a sufficient number of cases in children to be of statistical value in the estimation of prognosis. Nathhorst (1), in 1948, reviewed in great detail the clinical course and prognosis of 595 cases of pleurisy with effusion in Swedish children up to sixteen years of age who were followed for at least five years. Bentley, Grzybowski, and Benjamin (2) in 1954 reported 226 English children who were first seen in High Wood Hospital and were followed for six years. Other writers (3–6) report smaller series of children with effusion, the numbers ranging from 49 to 91. Possibly because the literature on pleurisy with effusion in children is so meager and that relating to adults so voluminous, many conclusions reached concerning the prognosis of pleurisy in adults have been accepted for the pediatric age group.

This paper will present data on a sizeable group of children with tuberculous pleurisy with effusion. Since most of these patients were seen before the era of antimicrobial therapy, information about them may help to establish the prognosis of the untreated case of pleurisy with effusion as a basis for later comparison with groups of children who have received antituberculous agents.

PLAN OF INVESTIGATION

Composition of Group

The present investigation was undertaken chiefly to determine the immediate and long-term prognosis of 202 consecutively observed cases of exudative tuberculous pleurisy seen in the Chest Clinic of the Children's Medical Service of Bellevue Hospital from October 1, 1930, through May 1, 1956.

All of the children were tuberculin positive and showed typical roentgenographic findings of effusion. In 137 children (67.8 per cent), the diagnosis was confirmed on thoracentesis by the finding of fluid consistent with the diagnosis of tuberculosis.

Children with effusions which occurred following pulmonary resection or in the course of treatment by pneumothorax have been excluded as well as children with tuberculous

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[1] From the Chest Clinic of the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University College of Medicine, New York, New York.

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empyema or caseous pleurisy. Also excluded are the few cases of effusion which occurred years after primary tuberculosis when the patient was no longer in the pediatric age range.

In the present group of 202 children with pleural effusion there were 26 patients in whom pleurisy was either accompanied or preceded by forms of tuberculosis of serious prognosis, such as generalized hematogenous tuberculosis. The 26 children will be discussed separately because of the probability that pleurisy did not play an important part in determining the ultimate outcome.

The remaining 176 of the 202 patients had no tuberculous complications prior to or at the time of the pleurisy which would indicate a serious prognosis. Presumably they all had primary pulmonary tuberculosis although 20 per cent showed no roentgenographic evidence of pulmonary or nodal involvement at the time of the pleurisy or later. Single manifestations of tuberculous disease, not in themselves of serious prognosis, were present at the time of the effusion in 8.5 per cent of the patients. It is the group of 176 children with which this report is primarily concerned in an attempt to evaluate the effect on prognosis of pleural effusion complicating primary tuberculosis in children.

Most of the children received periodic physical and roentgenographic examinations as part of the established procedure of follow-up study of the Children's Chest Clinic. A few were followed in other clinics or by private physicians but reports and roentgenograms were available for study.

Analysis of Group of 176 Patients

The seasonal incidence of the 176 cases of pleurisy with effusion is shown in figure 1. The greatest number of cases occurred in June and July, comprising one-third of the total cases. When grouped according to seasons it is obvious that autumn is the least likely time in which pleurisy with effusion develops.

The majority of the 176 patients had pleurisy on their first examination. In 34 patients, however, it was possible to calculate the interval from the date of the first diagnosis of tuberculosis to the occurrence of effusion (figure 2). Sixteen children developed pleurisy within three months and 21 within six months of the first diagnosis of tuberculosis; the longest interval was forty-one months.

The observation that pleurisy with effusion tends to occur as a relatively early complication of primary tuberculosis is further borne out by the fact that only 5 of the 176 patients had roentgenographic evidence of calcification of a primary complex at the time of the pleurisy.

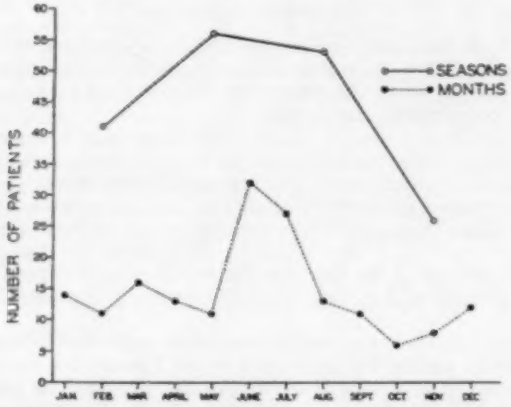

FIG. 1. Seasonal incidence of 176 consecutive cases of pleurisy with effusion

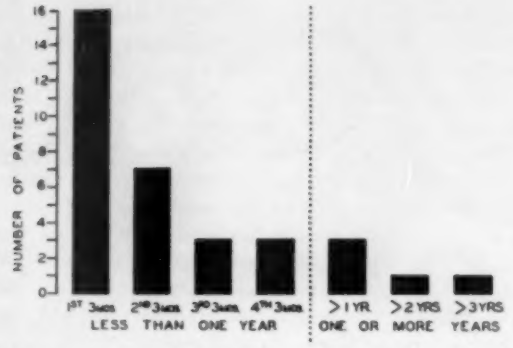

FIG. 2. Time interval between first diagnosis of tuberculosis and pleurisy in 34 cases

TABLE 1

AGES OF CHILDREN AT ONSET OF PLEURAL EFFUSION

	Age in Years													
	<1	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of children.....	2	9	12	22	14	25	15	14	16	19	13	13	8	4
Total.....	59					79					38			

Throughout the period of study the majority of the children came from families of low economic level. There were 68 U. S. white children in the group, 52 U. S. non-whites, 52 Puerto Ricans, 3 Chinese, and one Mexican. Although the total number of children with primary tuberculosis during the period of study was fairly evenly divided between males and females, there were 112 boys and only 64 girls in the group with evidence of pleurisy with effusion. Only one pair of siblings was present in this series. The ages of the patients at the time of their pleural effusions are listed in table 1.

As seen in table 1, 33.5 per cent of the total number of cases of pleural effusion occurred in those less than five years old. Forty-four and nine-tenths per cent of the pleural effusions manifested themselves in children five through nine years of age, and only 21.6 per cent of the total number of effusions occurred in the early adolescent years of ten through thirteen. During the period of this study children less than four years of age constituted about 65 per cent of the ward population. Since only 25.6 per cent of this age group developed pleurisy with effusion it is obvious that effusion is relatively uncommon in this age group.

OBSERVATIONS

Clinical Picture

The most common presenting symptoms were cough and chest pain. Fever was usually present, and in 61 cases accurate observations were available so that its duration could be measured; the average duration in these patients was

twenty-one days. Dyspnea was noted only 25 times. Nine patients were completely asymptomatic when the effusion was diagnosed roentgenographically. The clinical signs elicited were the classical ones described for pleural effusions. The average duration of the effusion in those patients in whom it could be measured was forty-eight days; the longest period observed was one hundred and fifty-six days. The effusion was considered absorbed when the dome of the diaphragm could be outlined roentgenographically. In three patients the effusion manifested itself within a few days of the appearance of a severe local reaction to a Mantoux test. One of these cases has been described previously (7).

As noted before, no children in this group of 176 patients had complications which would indicate a grave prognosis. Two children had roentgenographic evidence of spondylitis at the time of the pleurisy; one had tuberculous otitis media, and 2 had cutaneous tuberculosis. Evidence of a healed choroiditis was found in one child, two had phlyctenular conjunctivitis, and one child had erythema nodosum at the onset of the pleurisy. Tubercle bacilli were cultured on one occasion from the urine of a child who also showed increased leukocytes and a few casts but who was followed until the age of twenty-five and never developed any further evidence of renal involvement.

The diagnosis of serous meningitis was made at the onset of the effusion or shortly thereafter in 4 instances, and it is worthy of note that 2 of these children were in the small group cited above who had severe tuberculin reactions immediately preceding the effusion. A fifth child had serous meningitis immediately following a severe sunburn; six weeks later he developed tuberculous pleurisy with effusion. In the experience of the present writers (8), the occurrence of serous meningitis does not influence the prognosis adversely. The remaining patients comprising 91.5 per cent of the group of 176 children with pleural effusion accompanying primary tuberculosis had no tuberculous complications preceding or at the time of the effusion.

Roentgenographic findings: The effusion was on the right side in 92 instances; on the left, 77 times. There were 7 children with bilateral effusion. The relationship of the location of the primary focus, as determined by early roentgenograms and by evidence of calcification on later chest films, to the site of the effusions is shown in table 2.

Pleurisy with effusion occurred slightly more often on the right side than on the left. The effusion was on the same side as the primary focus in approximately

TABLE 2

RELATION OF SITE OF PRIMARY FOCUS ON EARLY ROENTGENOGRAM AND BY LATER CALCIFICATION TO THE SITE OF THE EFFUSION IN 169 CASES (EXCLUDING 7 BILATERAL EFFUSIONS)

	Number of Cases	Per Cent of Total	1° on Right		1° on Left		1° not Visualized	
			Number	Per cent	Number	Per cent	Number	Per cent
Effusion on right...	92	54.4	59	64.1	13	14.1	20	21.7
Effusion on left....	77	45.6	9	11.7	53	68.8	15	19.5

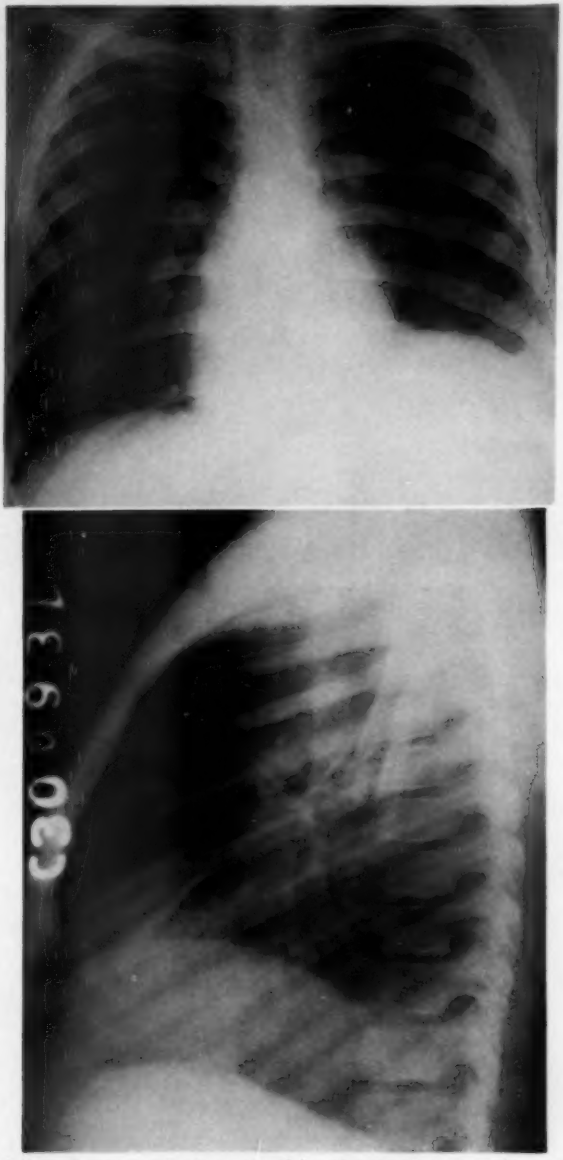

FIG. 3. Infrapulmonary effusion proved by thoracentesis in a boy of 11 years

two-thirds of the patients regardless of whether the effusion was on the right or left side. More than half of the children (98, or 56.1 per cent) had roentgenographic evidence of involvement of both parenchymal and nodal components of the primary complex. Forty (22.8 per cent) had definite enlargement of mediastinal nodes without parenchymal shadows or later parenchymal calcification, and only 2 children had parenchymal shadows later containing calcification without obvious involvement of regional nodes. No evidence of a primary complex was ever found even by later calcification in 35 (20 per cent) of the patients. Infrapulmonary effusion (9) was diagnosed in only one patient (figure 3).

In 5 of the 7 children with bilateral effusions, the left side was the first one involved; the interval between effusions was one to three months. One of these children had a tuberculous spondylitis; another, a serous meningitis at the time of onset of the first pleurisy. Otherwise there were no tuberculous complications at the time of the pleurisy. One patient developed chronic pulmonary tuberculosis four years after bilateral effusion.

Character of pleural fluid: Fluid was obtained by thoracentesis in 136 of the 176 cases and varied from yellow to amber in color; one effusion was frankly bloody on repeated taps. The fluid was usually clear, occasionally slightly turbid, and in the cases in which cell counts were done the number of leukocytes varied greatly, from 250 to 10,000 cells per cu. mm., always with a predominance of lymphocytes varying from 68 to 100 per cent. Tubercle bacilli were demonstrated by culture or guinea pig inoculation 24 times or in 17.7 per cent of the patients.

Follow-up Observation of 176 Patients

The duration of follow-up observation of the 176 patients tabulated according to age at the time of pleurisy is shown in table 3.

As shown in table 3, 141 (80 per cent) of the 176 patients have been followed longer than five years. Of the 35 under supervision for less than five years, 4 died less than five years after the pleurisy. Twenty-four children were seen so recently that the period of follow-up study is only from one through four years. Seven patients were lost to follow-up observation before five years had elapsed. Six of the 45 children followed five through nine years and 2 patients in each of the next groups are not under supervision at present. Thus, a total of 17 patients are either temporarily or permanently lost to follow-up study. The remaining

TABLE 3

DURATION OF FOLLOW-UP OBSERVATIONS ACCORDING TO AGE OF PATIENT AT TIME OF PLEURISY

Age at Onset of Pleurisy	< 5 years	5–9 years	10–14 years	15–19 years	> 20 years
Less than 5 years of age	12	12	16	11	8
5–9 years of age	14	16	22	17	10
10–13 years of age	9	17	5	7	—
	35	45	43	35	18

159 patients, (90.3 per cent of the 176) are still under supervision or the follow-up study has been terminated after the patients have reached a minimal age of twenty-one years.

A different method of tabulating the duration of follow-up observations in the 176 patients is shown in table 4.

As seen in table 4, 136 of the 176 patients (77 per cent) have been followed until the children were more than twelve years of age and 58 per cent have been followed after they have reached the age of sixteen.

Sequelae in 176 children with pleural effusion: Blunting of the costophrenic angles persisted for more than a year in 56 patients, or about one-third of the group of 176 children with pleurisy with effusion. In 48 of the 56 cases the costophrenic angle remained obscured throughout the follow-up period. The axillary pleura remained visible for more than one year in 100 patients. Serial roentgenograms were reviewed for at least five years following pleurisy with effusion in 115 patients, and 77 showed persistent thickening of the pleura throughout this period; in 66 patients the thickening remained visible during the entire period of observation up to twenty-two years.

Localized thickening of the pleura appearing as "pleural plaques" was seen in 22 instances but persisted for the duration of follow-up study only 15 times. Most of the plaques showed evidence of calcification and some did not appear roentgenographically until several years after the effusion.

Definite contraction of the hemithorax of various degrees was a sequela of the pleurisy in 13 patients. Treatment of empyema by oleothorax almost certainly contributed to the deformity in one instance. The size of the effusion and the age of the child at onset, or the amount of pleural fluid removed did not appear to be significant factors in producing this deformity. An extreme example is illustrated in figure 4.

Evidence of scoliosis was noted in 29 patients, being of minimal degree in 21, moderate in 6, and marked in 2 instances. In the cases of scoliosis of slight degree, it was believed that no definite causal relationship to the previous pleurisy could be demonstrated; in 12 instances the spinal convexity was toward the unaffected side but 8 times it was toward the original site of the pleurisy. One patient with minimal scoliosis had had bilateral effusions.

The spinal convexity was toward the unaffected side 4 of 5 times in children with previous unilateral pleurisy and moderate degrees of scoliosis and in both

TABLE 4

AGE REACHED BY 176 PATIENTS AT TIME OF MOST RECENT FOLLOW-UP INFORMATION

Age	Number of Patients
21–30 years	57
16–20 years	46
12–15 years	33
Less than 12 years	40

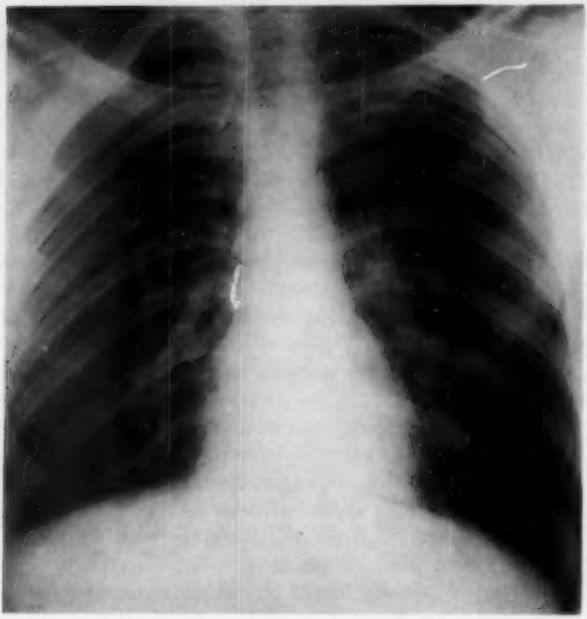

FIG. 4. Narrowing of interspaces following right pleurisy with effusion

patients with marked spinal deformity. Since a convexity toward the unaffected side conforms to the pattern of scoliosis which might be expected following pleurisy, it was assumed that most, if not all, of the deformities of moderate or marked degree were due to the preceding pleurisy. An illustrative case is shown in figure 5.

Tuberculous empyema followed the exudative pleurisy in only 2 instances in this group of 176 children. One boy, seven years of age, after repeated thoracenteses was finally treated by oleothorax and remains well twenty years later. A girl of five years of age, who had developed an effusion ten months after primary tuberculosis was diagnosed, apparently recovered from the subsequent empyema but died eight years later of tuberculous meningitis.

Extrapulmonary complications following pleurisy: Meningitis followed pleurisy with effusions in 5 instances, and peritonitis developed in one instance in a child who was convalescing from pleurisy. Further details are shown in table 5.

Chronic pulmonary tuberculosis following pleural effusion: There were 10 children who developed chronic pulmonary tuberculosis at intervals of six months to ten years and five months after pleurisy with effusion. All of these patients had roentgenographic evidence of primary tuberculosis. Details are shown in table 6.

The occurrence of later extrapulmonary complications in this group of 176 patients was 3.4 per cent; of meningitis, 2.8 per cent. The incidence of later

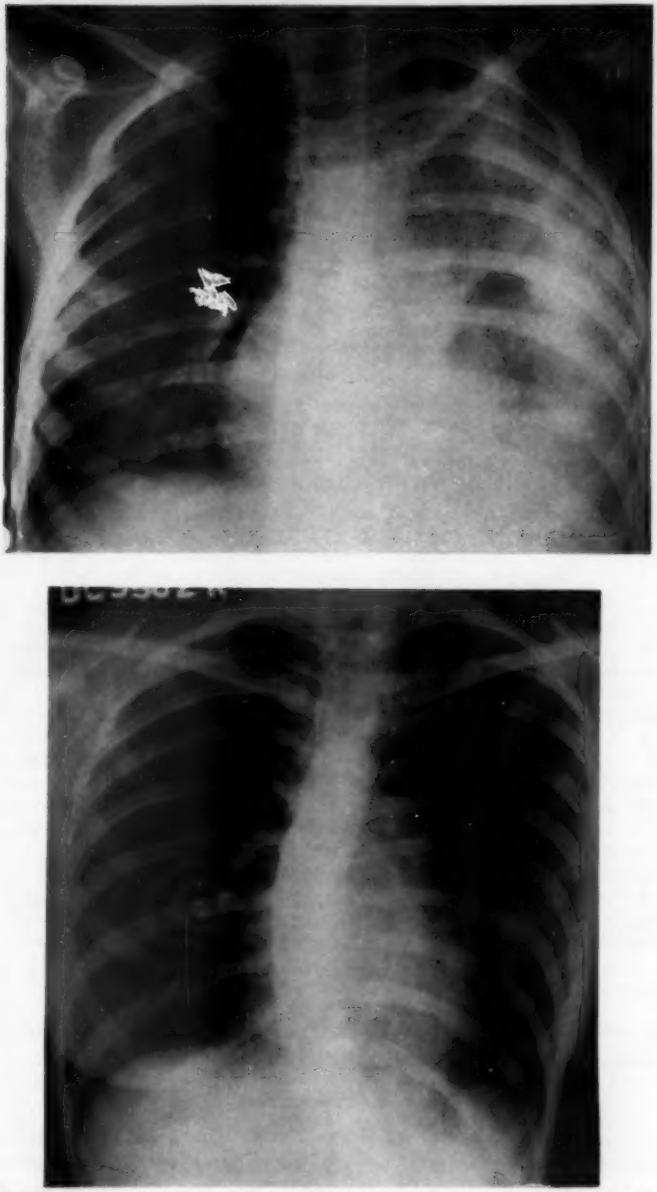

FIG. 5*A* (Top). Pleurisy with effusion and absence of scoliosis in a 5-year-old girl
B. Marked convexity to right following effusion in the same patient

TABLE 5

EXTRAPULMONARY COMPLICATIONS FOLLOWING PLEURISY

Complication	Race or Geographic Origin	Sex	Age at Time of Pleurisy	Time Interval Between Pleurisy and Complication	Outcome
			years		
1. Meningitis*	PR	F	5	3 years	Died
2. Meningitis	W	M	7	2 months	Died
3. Meningitis	W	M	5	2 months	Died
4. Miliary tuberculosis and meningitis	N	M	8	2 months	Died
5. Meningitis	W	M	3	2 months	Survivor, 13 years old†
6. Peritonitis	N	M	5	1 month	Well at 10 years, extensive calcification in chest and abdomen†

* Already described as having empyema preceding meningitis

† Received antimicrobial therapy for complication

TABLE 6

CHRONIC PULMONARY TUBERCULOSIS FOLLOWING TUBERCULOUS PLEURISY WITH EFFUSION IN 176 CASES

	Race	Sex	Age at Time of Pleurisy	Interval in Years to Chronic Pulmonary Tuberculosis	Outcome
1.	W	F	2	10 years, 5 months	Died at 13 years, 8 months*
2.	N	F	3	5 years, 11 months	Specific therapy and lobectomy, now 13 years old
3.	N	M	4	4 years, 11 months	Arrested, now 21 years old*
4.	W	M	8	8 years, 11 months	Arrested, then relapse; still on specific therapy at 22 years of age
5.	W	M	8	8 years, 4 months	Arrested, now 20 years old*
6.	N	F	9	6 months	Progressive pulmonary disease and tuberculosis of hip.* Died 12 years of age
7.	W	F	10	5 years, 2 months	Died at 23 years of age*
8.	N	M	11	5 years, 4 months	Arrested, 27 years of age*
9.	N	M	11	3 years, 6 months	Died at 15 years of age*
10.	N	F	13	1 year, 5 months	Died at 17 years of age*

* Before specific therapy was available

chronic pulmonary tuberculosis was 5.7 per cent. The death rate from tuberculosis of all forms following pleurisy with effusion was 5.1 per cent.

Specific Therapy

A total of 154 (87.5 per cent) of the 176 patients with pleural effusion were not treated. One hundred and twenty-one children with pleural effusion were observed before the era of specific therapy; in addition 33 patients who developed pleurisy after January 1, 1947, were not given antimicrobial therapy. Twenty patients received some form of antimicrobial therapy, most of them recently,

and to date none have developed complications. Six treated patients were less than four years of age, 7 were in the five- to nine-year age group and 7 were ten to thirteen years of age. In addition, 2 children were in the meningitis prophylaxis study of the U.S.PHS and received pills for a year, but it is not yet known whether they received isoniazid or placebo.

One 5-year-old girl was given specific therapy because steroids were used in the treatment of her pleural effusion. In this case a rapid defervescence and absorption of fluid were observed. Otherwise no striking effect of antimicrobial therapy on the duration of effusion or of the accompanying fever was seen. The number of treated patients is much too small to be of significance in the evaluation of specific therapy.

Pleural Effusions Associated with Tuberculous Complications Having a Serious Prognosis

In addition to the 176 children already discussed there were in the consecutive case group 26 patients with pleural effusions who had other evidences of tuberculosis frequently associated with an unfavorable prognosis. The ages of these patients ranged from five months to thirteen years and, in contrast to the distri-

TABLE 7

FIVE CHILDREN WITH PLEURAL EFFUSION ACCOMPANIED OR PRECEDED BY CHRONIC PULMONARY TUBERCULOSIS

	Sex	Race	Age at Time of Pleurisy	Associated Tuberculosis	Outcome
1.	F	W	8	Moderately advanced CPT* plus pleurisy, progressive CPT after pleurisy.	Died of tuberculosis 4 years after pleurisy†
2.	M	Chinese	11	Minimal CPT plus pleurisy plus congenital heart disease. CPT stationary for 3 years after pleurisy, then progressive. Given specific therapy leading to arrest of CPT.	Died 5 years after pleurisy, following cardiac surgery
3.	M	N	12	Minimal CPT plus pleurisy followed by empyema; pleurectomy 17 months later. Peritonitis and reactivation of pulmonary disease 33 months after pleurisy.	Died of tuberculosis 3 years after pleurisy†
4.	F	W	12	Minimal CPT plus resection of submental caseous node; dactylitis 1 month later, pleurisy on left 3 months later, followed in 17 months by pleurisy on right. Generalized miliary tuberculosis 20 months after first effusion. Treated successfully with sulfone (Promizole®) but followed by multiple areas of skeletal tuberculosis, later treated with streptomycin.	Alive and well at 25 years of age
5.	F	N	13	Minimal CPT for 3 years before pleurisy. Progressive CPT after pleurisy. Terminal meningitis.	Died 17 months after pleurisy†

* CPT—chronic pulmonary tuberculosis

† Before specific therapy

TABLE 8

TWENTY-ONE CHILDREN WITH PLEURAL EFFUSION ASSOCIATED WITH EXTENSIVE TUBERCULOUS DISEASE (EXCLUDING CHRONIC PULMONARY TUBERCULOSIS)

	Sex	Race or Geographic Origin	Age at Time of Pleurisy	Other Evidences of Tuberculosis	Outcome
1.	M	PR	6 months	Miliary tuberculosis preceding effusion by 1 month. Severe endobronchitis, bronchogenic spread.	Treated with sulfone (Promizole). Died at 1 year of age
2.	M	PR	6 years	Miliary tuberculosis with bilateral pleural effusion; spondylitis, chorioretinitis. Urine culture positive for tubercle bacilli	Treated with sulfone for 3 years. Recovery. Bilateral renal tuberculosis at 15 years, surviving at 19 years.
3.	F	PR	1 year	Miliary tuberculosis	Treated with isoniazid and sulfone. Arrested at 3 years of age.
4.	M	N	8 years	Hematogenous tuberculosis—bilateral pleural effusion, pericarditis, peritonitis, lymphadenopathy ++++. PM: caseating pleurisy, peritonitis, pericarditis.	Died, 4 months after pleurisy.*
5.	M	N	11 years	Hematogenous tuberculosis, lungs, nodes, peritoneum.	Died 10 weeks after pleurisy.*
→ 6.	F	W	9 years	Hematogenous tuberculosis, lungs, nodes, peritoneum, spleen.	Died 2 months after pleurisy.*
7.	M	N	11 years	Hematogenous tuberculosis, pharynx, nodes, liver, spleen, sternum → caseating pleura → meningitis.	Died 2 years after pleurisy.*
8.	M	N	9 years	Hematogenous tuberculosis, lungs, nodes, peritoneum, liver, spleen.	Died 1 month after pleurisy.*
9.	F	N	22 months	Hematogenous tuberculosis, lungs, elbow, skin, liver, spleen, pericardium, cortical tuberculoma with paresis and serous meningitis.	Died 6 months after pleurisy.*
10.	M	N	3 years	Hematogenous tuberculosis, lungs, skin, bone, peritoneum, epididymitis. PM: caseating pleura, peritoneum, pericardium.	Died 1 year after pleurisy.*
11.	F	N	7 years	Hematogenous tuberculosis, lungs, nodes, peritoneum, pericardium, skin.	Died 5 months after pleurisy.*
12.	F	PR	10 years	Hematogenous tuberculosis, lungs, peritoneum, nodes, liver, spleen.	Died 9 months after pleurisy.*
13.	M	PR	2 years	Hematogenous tuberculosis, lymphadenopathy, otitis.	Apparent arrest; died at 8 years of age in Puerto Rico of "tuberculosis."*

TABLE 8—*Continued*

	Sex	Race or Geographic Origin	Age at Time of Pleurisy	Other Evidences of Tuberculosis	Outcome
14.	M	N	2 years	Generalized skin tuberculosis and phlyctenular conjunctivitis preceding pleurisy with effusion by 17 months. Miliary tuberculosis, bone tuberculosis, urine culture positive for tubercle bacilli, and meningitis at 12 years.	Specific therapy for miliary tuberculosis and meningitis. Well at 16 years.
15.	M	W	3 years	Cervical adenitis, serous meningitis, splenomegaly preceding effusion by 15 months. Recurrent periods of high fever, ?peritonitis.	Specific therapy (isoniazid) begun 8 months before pleurisy, later treated with all available antimicrobials; ?arrested at 7 years.
16.	M	N	9 years	Peritonitis, mesenteric adenitis preceding pleurisy by 1 year → extensive calcification in abdomen.	Alive and well at 23 years.*
17.	M	PR	12 years	Caseous peritonitis (operation), lymphadenopathy preceding pleurisy by 13 months. Dactylitis occurring with pleurisy.	Alive and well at 26 years.*
18.	M	PR	3 years	Supraclav. and axillary nodes ++++. Tuberculosis of skin, epididymis, peritoneum, phlyctenular conjunctivitis followed by effusion 11 months after first diagnosis.	Alive and well at 18 years.*
19.	M	N	10 years	Cervical spondylitis and radiculitis and arachnoiditis (operation) → quadriplegia.	Died 4 months after pleurisy.*
20.	M	N	2 years	Tuberculous bronchopneumonia, right and left. PM: caseous bronchopneumonia due to erosion of node into bronchus.	Died 2 months after pleurisy.*
21.	F	N	7 years	Cavitating primary tuberculosis, right, and effusion, right → effusion, left, 3 months → chronic pulmonary tuberculosis in location of primary at 10 years of age with enteritis and laryngitis.	No initial specific therapy. Apparent arrest. Streptomycin for chronic pulmonary tuberculosis. Survival at 18 years of age.

*No specific therapy.

bution of the group of 176 patients previously described, most of the children were in the youngest group or were adolescents. There were 9 patients less than five years of age, 8 in the five through nine group, and 9 in the group of ten through thirteen years of age. There were 17 males and 9 females and more than half the patients (14) were U. S. non-whites.

Five patients had roentgenographic evidence of chronic pulmonary tuberculosis preceding or accompanying the pleurisy and only one survived. Further details are shown in table 7.

Of the remaining 21 children, 18 had evidences of generalized tuberculosis of hematogenous origin accompanying or preceding the onset of pleurisy with effusion, and 3 patients had other forms of tuberculosis associated with an unfavorable prognosis. More details of these 21 children are given in table 8.

The 21 patients whose histories have been outlined in table 8 have been discussed separately because it was evident at the time when each had pleurisy with effusion that the associated or preceding tuberculous disease indicated a poor prognosis for life or for complete recovery. Seventeen of the patients (65.4 per cent) died. During the pre-chemotherapy era the mortality rate from miliary tuberculosis was close to 100 per cent on the wards of the Children's Chest Clinic of Bellevue Hospital, and 2 of every 3 children with protracted hematogenous tuberculosis or cavitating primary tuberculosis died. Consequently the pleurisy may have had little influence on the prognosis in this group.

Discussion

The poor prognosis of pleurisy with effusion in adults has been stressed repeatedly. Thompson (10) found that 25 per cent of 190 patients with primary pleurisy with effusion had developed systemic tuberculosis within five years. Most of the lesions were pulmonary. Sibley (11) reported 200 consecutive cases of pleurisy with effusion in young adults, 51 per cent of whom developed tuberculosis, largely pulmonary. Roper and Waring (12) followed 141 young male adults for at least five years and reported finding 92 (65 per cent) with active tuberculosis, pulmonary in 73. The majority of cases were found within three years of the pleurisy. Thus, in these series dealing exclusively with adults, 25 to 65 per cent of the patients with pleurisy with effusion later developed tuberculosis, chiefly pulmonary.

The results of follow-up observation of patients whose pleurisy with effusion occurred during childhood are in marked contrast to the statistics quoted for adults. Nathhorst (1) included children up to sixteen years of age in his group but, in spite of the inclusion of patients beyond the usual pediatric age range, he found that only 18.8 per cent developed tuberculous complications; 8.9 per cent of his group died of tuberculosis. The mortality from extrapulmonary tuberculosis was roughly the same whether pleurisy had occurred when the patient was less or more than ten years of age; but more children died of chronic pulmonary tuberculosis who had pleurisy when ten years of age or older. Bentley and associates (2) reported a mortality rate of 2.6 per cent and found that 7 per cent of their patients with pleurisy later developed chronic pulmonary tuberculosis; the total morbidity from all forms of tuberculosis was 11.5 per cent. In the group of 176 patients from Bellevue Hospital the total mortality rate was 5.1 per cent, higher than Bentley's but lower than that reported by Nathhorst.

Ten of the 176 patients (5.7 per cent) developed chronic pulmonary tuberculosis. In a group of 1,000 consecutive cases of pulmonary primary tuberculosis of comparable age distribution under study in the same clinic, the later incidence

of chronic pulmonary tuberculosis in the survivors has been 8.9 per cent. Since only 5.7 per cent of the children with pleurisy with effusion developed later chronic pulmonary tuberculosis, it is obvious that pleurisy accompanying primary tuberculosis in children does not increase the risk of developing later pulmonary tuberculosis.

It must be concluded that the prognosis of pleurisy with effusion in children is very much better than it is in adults. Why this should be is not clear. All reported series in adults have a high percentage of patients with essentially normal roentgenograms aside from the pleurisy, and yet a considerable number of the patients subsequently develop tuberculosis. In the children's series from Bellevue Hospital, only 20 per cent showed no roentgenographic evidence of primary tuberculosis at the time of the pleurisy; and not one of these later developed chronic pulmonary tuberculosis. In the group of 176 patients, the age at onset of the effusion seems to have a definite bearing on outcome. Morbidity in the zero- to four-year-old group was 6.8 per cent; in the five- to nine-year-old group, 10.1; and in the children ten to thirteen years old, 10.5. This difference is due to the increased risk of developing chronic pulmonary tuberculosis as the child grows older. In the present group, 4.3 per cent of those less than ten years of age at the time of pleurisy developed later chronic pulmonary tuberculosis as against 10.5 per cent in children more than ten years of age at the time of pleurisy.

The clinical picture of tuberculous pleurisy with effusion in this group of children did not appear to deviate in any important respect from the accepted one. The majority of patients presented with an acute illness, with cough and chest pain as the most common symptoms, fever usually occurring at the onset of illness and continuing for a varying period; a few children were asymptomatic at the time when the roentgenographic or physical examination gave evidence of an effusion.

The fluid obtained by thoracentesis was usually of the type recognized as characteristic for tuberculous pleurisy with effusion, and in only one instance when repeated thoracenteses produced only sanguineous fluid did the problem of differential diagnosis arise. The character of the fluid did not aid in the prognosis. Even in the group of 26 children with obviously poor prognosis who had many other evidences of tuberculosis of hematogenous origin, the initial thoracentesis yielded the usual type of clear or slightly cloudy fluid with a moderate number of cells, predominantly lymphocytes. Yet in some instances the disease progressed so rapidly that on post-mortem examination only two months later the pleurae and often the pericardium and peritoneum were covered with a massive layer of caseation.

The seasonal incidence in the series from Bellevue Hospital is similar to that frequently reported.

Wallgren (13) has suggested that pleurisy may be a later complication of primary tuberculosis than other sequelae, notably tuberculous meningitis, but this timetable is not confirmed by the data in the present series which suggests that pleurisy, like meningitis, is usually an early complication in children.

As in most reported series in children, there is a preponderance of males in the

series here presented. Because of the emphasis often laid on the serious prognosis of bilateral effusions in adults, it should be mentioned again that 6 of the 7 children with bilateral effusions in the group of 176 patients had no complications; the seventh, who later developed chronic pulmonary tuberculosis, recovered without specific therapy and has remained well.

No support for any single theory of the pathogenesis of pleurisy with effusion is available in the present series. The pleurisy was homolateral in approximately two-thirds of the patients with a visible focus of pulmonary primary tuberculosis, lending support to the theory so clearly stated by Rich (14), and recently again stressed by Stead (15), that pleurisy with effusion arises by direct spread from a subpleural focus. Supporting the theory that this initial lesion on the pleura may originally have been of hematogenous origin are the 15 cases of protracted hematogenous tuberculosis represented in the group of 26 patients with a poor prognosis aside from pleurisy with effusion. Certainly a hematogenous origin is suggested in individual cases, such as the boy who, following surgery for caseous peritonitis, developed simultaneous dactylitis and pleural effusion. The histories of at least four children who developed pleurisy very soon after severe reactions to tuberculin tests suggest that the theory that an allergic reaction plays a part in the production of pleurisy with effusion may have some basis in fact. The association of serous meningitis with the severe tuberculin reactions in some instances would also support this hypothesis.

Thickening of the pleura following effusion occurred in a high percentage of cases and often remained visible roentgenographically for long periods of time. However, in the series of patients presented there is no evidence that thickened or adherent pleura caused any symptoms of pulmonary insufficiency in those who were followed into adult life. The incidence of a moderate or severe degree of scoliosis following pleurisy was 4.5 per cent which is too high to be accounted for as idiopathic scoliosis, suggesting that physical factors during or following pleurisy with effusion may have caused the deformity. Repeated pulmonary function studies as part of the follow-up study of children who have recovered from pleurisy with effusion would be advisable to obtain information regarding the risk of pulmonary disability following pleural effusion.

Specific treatment is indicated for pleurisy with effusion, as it would be for any complication of primary tuberculosis in a child. However, no claims have been made that specific therapy causes early resolution of the fluid or hastens defervescence. The addition of steroid therapy to antimicrobial agents seems justified since both the local and febrile response are apparently satisfactory (16). If it can be proved that combined steroid and antimicrobial therapy will prevent adherent pleura, this should certainly be the treatment of choice. Adequate therapy with isoniazid should prevent the occurrence of meningitis as a complication of pleurisy. Whether it will prevent the development of chronic pulmonary tuberculosis many years later is a question which will be solved only by the careful follow-up observation of groups of treated patients. The recent report by Falk and Stead (17) is encouraging; it shows a marked reduction in the incidence of later tuberculous complications in adults treated for pleurisy with effusion by antimicrobial agents. A comparable reduction in complications

will be more difficult to demonstrate in children since the incidence of later tuberculosis is so much lower in untreated children than in adults.

Summary

A group of 202 consecutive cases of pleurisy with effusion, presumably tuberculous, is reported. All of the patients had positive tuberculin tests. In 176 of the children, 87 per cent of whom received no specific therapy, the effusion was not associated with any form of tuberculosis with a serious prognosis, and this group is analyzed in detail.

Effusions occurred most commonly in the spring and summer, least often in the autumn; they were relatively early complications of primary tuberculosis, usually occurring within three to six months after the onset of the primary infection. Boys were affected almost twice as often as girls. Most of the cases of pleurisy (44.9 per cent) occurred in the five- to nine-year age group; 33.5 per cent in those children less than five years old, and 21.6 per cent in those ten through thirteen years old. Effusions occurred on the right side slightly more often than on the left and were on the same side as the primary focus in about two-thirds of the cases. No roentgenographic evidence of primary tuberculosis other than the effusion was found in 20 per cent. Evidence of pleural thickening was present in more than half the patients for at least five years after the effusion and persisted in the majority of them for the duration of follow-up observations. The effusion was considered contributory to the moderate or severe scoliosis which developed later in 4.5 per cent of the group.

Chronic pulmonary tuberculosis developed later in 5.7 per cent of the children. The incidence was nearly twice as high in those patients who were ten years of age or older at the onset of pleurisy. These comparatively low figures are in marked contrast to those commonly reported for adults. Extrapulmonary tuberculous complications developed in a further 3.4 per cent of the group. The total mortality from all causes was 5.1 per cent. Age appeared to have a definite bearing on the prognosis in that the morbidity in the zero- to four-year-old age group was 6.8 per cent, 10.1 per cent in the five- to nine-year-old group, and 10.5 in those ten to thirteen years of age. The difference in the percentage of morbidity was due to the increased risk of developing chronic pulmonary tuberculosis as the child grew older.

In the entire group of 202 patients, pleurisy with effusion was associated with other forms of tuberculosis of serious prognosis, i.e., generalized hematogenous tuberculosis, in 26 patients. The mortality in this group was 65.4 per cent and it is probable that the pleurisy was not an important factor in creating this high rate.

Sumario

La Pleuresía Tuberculosa con Derrame en los Niños; Estudio de 202 Casos con Referencia Particular al Pronóstico

Preséntase un grupo de 202 casos consecutivos de pleuresía con derrame, presuntamente tuberculosa. Todos los enfermos acusaron reacciones positivas a la tuberculina. En 176 de los niños, 87 por ciento de los cuales no habían recibido terapéutica específica, el der-

rame no se vinculaba con ninguna forma de tuberculosis de pronóstico grave, y este grupo se analiza a fondo.

Los derrames se presentaron más comúnmente en la primavera y el verano, y menos a menudo en el otoño; fueron complicaciones relativamente tempranas de la tuberculosis primaria, ocurriendo habitualmente en término de tres a seis meses de la iniciación de la infección primaria. Los varones se afectaron casi dos veces más que las mujeres. La cifra mayor de los casos de pleuresía (44.9 por ciento) fué en el grupo de cinco a nueve años de edad; 33.5 por ciento en los niños de menos de cinco años; y 21.6 por ciento en los de diez a trece años inclusive. Hubo derrames en el lado derecho un poco más a menudo que en el izquierdo, quedando del mismo lado que el foco primario en unas dos terceras partes de los casos. En 20 por ciento no se descubrieron signos radiográficos de tuberculosis primaria aparte del derrame. Hubo signos de espesamiento pleural en más de la mitad de los enfermos a lo menos por cinco años después del derrame, persistiendo en la mayoría de ellos durante el período de observación. En 4.5 por ciento del grupo se consideró que el derrame contribuyó a la escoliosis moderada o grave que se presentó después.

En 5.7 por ciento de los niños apareció más tarde tuberculosis pulmonar crónica. La incidencia fué casi el doble en los enfermos que tenían diez años o más al iniciarse la pleuresía. Estas cifras comparativamente bajas se hallan en decidida contraposición a las comunicadas habitualmente para los adultos. Hubo complicaciones tuberculosas extrapulmonares en otro 3.4 por ciento del grupo. La mortalidad global por todas causas fué de 5.1 por ciento. La edad pareció guardar una relación bien definida con el pronóstico porque la morbidad fué de 6.8 por ciento en el grupo de cero a cuatro años de edad, de 10.1 por ciento en el de cinco a nueve años y de 10.5 por ciento en los niños de diez a trece años. La diferencia en el porcentaje de morbidad se debió al mayor riesgo de contraer tuberculosis pulmonar crónica a medida que subía la edad del niño.

En todo el grupo de 202 enfermos, la pleuresía con derrame se asoció con otras formas de tuberculosis de pronóstico grave, es decir, tuberculosis hematógena generalizada, en 26 enfermos. La mortalidad en este grupo ascendió a 65.4 por ciento, siendo probable que la pleuresía no fuera un factor importante en la creación de ese elevado coeficiente.

Resume

La pleurésie tuberculeuse avec épanchement chez l'enfant: Une étude sur 202 cas du point de vue particulier du pronostic

Un groupe comportant une série de 202 cas de pleurésie avec épanchement, supposée d'origine tuberculeuse, est rapportée. Les tests à la tuberculine étaient positifs chez tous les malades. Sur un nombre de 176 enfants, 87% d'entre eux ne reçurent aucune médication spécifique, l'épanchement n'était associé à aucune forme de tuberculose d'un pronostic sévère; ce groupe est analysé en détail.

L'épanchement survenait le plus souvent au printemps et en été, moins souvent en automne; il était une complication relativement précoce d'une tuberculose primaire et se produisait habituellement dans les trois à six mois après la primo-infection. Les garçons étaient atteints presque deux fois plus que les filles. La plupart de ces cas de pleurésie (44,9%) survenaient dans la groupe de 5–9 ans; 33,5% de ces enfants avaient moins de cinq ans et 21,6% avaient de dix à treize ans. L'épanchement apparaissait du côté droit un peu plus souvent que du côté gauche et il siégeait du même côté que le foyer primaire dans deux tiers des cas environ. En dehors de l'épanchement, les radiogrammes ne montraient aucun signe de tuberculose dans 20% des cas. L'épaississement de la plèvre était présent chez plus de la moitié des patients pendant au moins cinq ans après l'épanchement et il persistait chez la majorité d'entre eux pendant toute la durée de la période d'observation. L'épanchement était considéré comme un facteur participant à la scoliose modérée ou sévère qui s'est constituée ultérieurement chez 4,5% des membres du groupe.

La tuberculose pulmonaire chronique s'est développée ultérieurement chez l'enfant dans 5,7% des cas. L'incidence était presque du double chez les malades qui étaient âgés

de dix ans ou plus au moment où la pleurésie est apparue. Ces chiffres comparativement faibles sont nettement différents de ceux habituellement rapportés chez l'adulte. En outre, des complications tuberculeuses extrapulmonaires se sont développées dans 3,4% des cas. La mortalité totale pour toutes causes était de 5,1%. L'âge paraissait influencer nettement le pronostic, en ce sens que la morbidité dans le groupe de 0–4 ans était de 6,8%, de 10,1% dans le groupe 5–9 ans et de 10,5% dans le groupe 10–13 ans. L'écart dans le pourcentage de morbidité était imputable à l'accroissement du risque d'évolution de la tuberculose pulmonaire chronique avec l'âge.

Chez 26 malades parmi le groupe entier des 202 malades, la pleurésie avec épanchement était associée à d'autres formes de tuberculose d'un pronostic grave, c'est-à-dire la tuberculose hématogène généralisée. Dans ce groupe, la mortalité était de 65,4% et il est probable que la contribution de la pleurésie à la création de ce taux élevé n'était pas importante.

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FILTRATION OF MYCOBACTERIA FROM ORGANIC SOLVENTS[1]

ALFRED J. CROWLE

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INTRODUCTION

It has been generally recognized for decades that animals vaccinated with killed or attenuated tubercle bacilli acquire protection against tuberculous infection. This has spurred vigorous attempts to separate immunogenic extracts from tubercle bacilli. It has been suggested that certain lipids of tubercle bacilli have varied and remarkable biologic activities, but unqualified agreement on which types of lipids are active has not been achieved. This can be attributed largely to the physical difficulty of separating the bacilli from their extracted lipids and, especially, of proving that the separation is complete. Without such proof, otherwise acceptable results lose much of their validity and confusion is generated.

Generally, lipoidal extracts are decontaminated by filtration or centrifugation used singly or in combination. By its nature, centrifugation can never be as certain as filtration. Conflicting experimental results recorded in the literature indicate that investigators often have been unaware of the unusual difficulties encountered in working with bacteria whose dry weight is about one-third lipid. These difficulties have not been so much with aqueous extracts as with organic solvent extracts; whereas the ability of bacteria-retaining filters to remove mycobacteria from water is well documented (1), opinions differ regarding their filtration from solvents of low polarity such as ether or chloroform (2–7). These differences of opinion might not exist were the tests for bacillary contamination of the extracted lipids more certain.

Hitherto, the test of choice has been microscopic examination of stained extracts, but this method has serious shortcomings. Acid-fast lipids can obscure bacilli or be mistaken for them; nonacid-fast bacilli go uncounted although they may retain important biologic properties.

In vivo infection tests for contamination of aqueous extracts with living, virulent bacilli can be very sensitive, but they are not sensitive for organic solvent extracts, for these solvents can kill or attenuate the bacilli (2, 8, 9). Moreover, even though a solvent were completely harmless to bacillary virulence, tuberculous lesions might not be invariably induced in guinea pigs, a most sensitive and available laboratory animal, by injection of very few tubercle bacilli (19). Two other technical disadvantages also must be considered. Test animals might not tolerate the large amounts of organic solvents which should be tested. Provided the animals could tolerate such solvents, contaminating bacilli would remain within the animal and be subject to the action of a solvent for a long time after it had been injected, since they are naturally hydrophobic and the solvent could not mix with water in the body or evaporate. To avoid

[1] From the Colorado Foundation for Research in Tuberculosis, and University of Colorado Medical School, Denver, Colorado.

this, filtrates would have to be dried and any sediment from them resuspended in water for injection, thus greatly increasing the chances for loss of the very few bacilli that might have escaped filtration. Other criteria for bacillary contamination, such as tuberculin allergy induction, are relatively insensitive and may be obscured by the activity of the extract itself.

Such testing difficulties have prevented a much needed incisive examination of whether common bacteria-retaining filters can withhold mycobacteria suspended in organic solvents. If these bacteria could be suspended in solvents unable to kill them, the suspensions filtered, and the filtrates tested for living bacilli on culture media sensitive enough to detect single viable units, accurate information would become available and the existing confusion would be considerably mitigated. This paper reports such filtration experiments performed with heavy suspensions of *M. smegmatis* and *M. tuberculosis* in organic solvents which are proved harmless for them.

Materials and Methods

Several preliminary experiments made use of the saprophyte *M. smegmatis* rather than tubercle bacilli because it is much safer and easier to work with in preparing and testing suspensions in volatile organic solvents. *M. smegmatis* grows rapidly and luxuriantly on a simple medium, yet it closely resembles *M. tuberculosis* physically. Later experiments utilized human tubercle bacilli, strains H37Rv and H37Ra.

Smegma bacilli to be tested were cultured for forty-eight hours at 37°C. on Sauton medium; test cultures and counts were made on Difco nutrient agar medium containing 5 per cent glycerol. Suspensions of *M. tuberculosis* were prepared from the surface pellicle of two weeks' growth at 37°C. on Kirchner medium, containing 1 per cent dextrose and 0.5 per cent Difco proteose-peptone. Counts and cultures were made primarily on Dubos oleic-acid–albumin agar.

Survival of smegma bacilli in methanol, 95 per cent ethanol, acetone, ethyl ether, ethyl acetate, chloroform, carbon tetrachloride, *o*-dichlorobenzene, benzene, toluene, xylene, petroleum ether (30–60°C., boiling point), pentane, cyclohexane, *n*-heptane, ligroin, and light mineral oil was investigated, not to determine the mycobactericidal efficacy of the solvents, but to find one or more solvents which would be harmless enough for mycobacteria to permit the desired filtration experiments. Although the method for evaluating the effects of these solvents was necessarily too crude to yield quantitative results, because bacilli were suspended in organic solvents each with its own suspending characteristics, it was considered adequate to indicate which solvents could be used. Solvents generally conceded to be strongly mycobactericidal were included because occasionally virulent tubercle bacilli exposed to one or more of these solvents have been reported to cause progressive tuberculosis in experimental animals (10, 11). Moreover, the effects of these solvents served for comparison with those of moderately toxic and nontoxic solvents.

A loopful of bacillary pellicle blotted with filter paper was ground vigorously in a few drops of solvent with a heat-sterilized glass rod, and then more solvent was added slowly with further grinding to make a total of 6.0 ml. The suspensions, deposited in screw-capped tubes, were immersed in running tap water (22°C.) for the duration of a survival experiment. They were shaken vigorously occasionally, and immediately before sampling.

For filtration experiments, freshly harvested bacilli were suspended at a concentration of 2.4 mg. per ml., moist weight, in one or each of the solvents, heptane, cyclohexane, pentane, and petroleum ether, by grinding them with a glass rod and a Ten Broeck tissue grinder.[2]

[2] Numerical estimation of bacilli suspended in each solvent was not practicable because of the differing characteristics of the solvents. Prior enumeration by means of a detergent-containing medium also was impracticable because water-soaked bacilli from such a medium would not suspend well in nonpolar solvents.

Three or more of the following filters were tested with portions of each suspension: fritted glass ultrafine (UF) porosity, bacteria-retaining Seitz, Mandler testing to 14 pounds, MF membrane filter disk[3] set in a Swinney syringe filter, two layers of Whatman grade 3 filter paper clamped between rubber gasketed filter components.

Half milliliter samples of survival and filtration test fluids were pipetted onto agar gel medium in Petri dishes and spread by rotation. The solvents were evaporated from inoculated plates by incubating them with their lids ajar for about ten minutes at 37°C. Several plates were then enclosed in a can together with a ball of water-soaked cotton and incubated at 37°C., for four to six days for smegma cultures, and for two to four weeks for H37Rv and H47Ra cultures.

Since filtration must either fail or succeed in producing an uncontaminated filtrate, only undiluted samples were plated and therefore each plate was recorded according to whether colonies of mycobacterium appeared. Control plates inoculated with undiluted, unfiltered suspensions were included in each experiment. To be of practical use for filtration tests, organic solvents should have no more lethal effect than water upon the bacilli. Therefore, they were compared with distilled water and the results were recorded in five degrees of growth as shown in tables 1 and 2.

Observations

Suspensions of *M. smegmatis* were kept at 22°C. for two days in various organic solvents and in distilled water. Half-milliliter undiluted samples were plated immediately after the suspensions were prepared and four, twenty-four, and forty-eight hours later. In the approximately ten minutes allowed for solvents to evaporate from the inoculated agar, *o*-dichlorobenzene evaporation was incomplete, and light mineral oil did not evaporate at all; consequently, bacilli in these two solvents remained exposed to them during subsequent incubation. The results of two experiments with various solvents are summarized in tables 1 and 2.

It is apparent that heptane, cyclohexane, pentane, petroleum ether, and light mineral oil (all saturated hydrocarbons) did not kill the smegma bacilli rapidly, if at all. All of these but light mineral oil are highly volatile and therefore were employed in the filtration experiments reported below.

Ligroin[4], because it is a petroleum distillation product resembling petroleum ether but having a higher boiling point, was not expected to kill these bacilli, but its lethal effect, shown in table 1, was confirmed in a separate experiment.

As recorded in table 2, no growth appeared on any twenty-four hour sample-plates. These plates had been incubated in a can together with *o*-dichlorobenzene samples. Vapor from this chemical not only prevented growth on the other plates in the can, which should have shown it abundantly, but also killed all bacilli on one of them (pentane). Upon further incubation in a fresh atmosphere these plates produced fewer colonies than analogous forty-eight hour sample-plates and one grew no colonies at all. Therefore, both liquid *o*-dichlorobenzene and its vapor were found to be lethal for the smegma bacilli.

The harmlessness of saturated hydrocarbons provided an excellent opportunity to examine by *in vitro* culture tests the ability of bacterial filters to remove mycobacteria from organic solvent suspensions. For the experiment reported in table 3, suspensions of 2.4 mg. of *M. smegmatis* per ml. in pentane, cyclohexane,

[3] Hydrosol Assay type made by the Millipore Filter Corporation, Watertown 72, Mass.
[4] Produced by the Matheson Company, East Rutherford, N. J.

TABLE 1

GROWTH OF MYCOBACTERIUM SMEGMATIS EXPOSED TO VARIOUS ORGANIC SOLVENTS

Solvent	Hours of Exposure			
	0	4	24	48
Toluene	3*	2	—	—
Chloroform	—	—	—	—
Petroleum ether	4	4	4	3
Carbon tetrachloride	1	—	—	—
Benzene	2	—	—	—
Ligroin	3	—	—	—
Ethyl ether	1	1	—	—
Acetone	—	—	—	—
Ethyl acetate	—	—	—	—
Ethanol	—	—	—	—
Methanol	—	—	—	—
Distilled water	4	4	4	3

* Numerical values indicate intensity of growth:
4: profuse and confluent; 3: uncountable, but discrete; 2: between 10 and 100 colonies per plate; 1: less than 10 colonies per plate; —: no colonies.

TABLE 2

GROWTH OF MYCOBACTERIUM SMEGMATIS EXPOSED TO VARIOUS ORGANIC SOLVENTS; LETHAL EFFECT OF O-DICHLOROBENZENE VAPOR

Solvent	Hours of Exposure			
	0	4	24	48
Light mineral oil	4*	4	(—)†	4
Xylene	—	—	(—)	—
Pentane	4	4	(—)	4
Cyclohexane	4	4	(—)	4
Heptane	4	4	(—)	3
Petroleum ether	4	4	(—)	3
o-dichlorobenzene	—	—	—	—

* Numerical values indicate intensity of growth (*cf.* table 1).
† No growth on first incubation.

petroleum ether, and heptane were filtered, within an hour of preparation, through each of three or more of fritted glass, Seitz, Mandler, and MF filters and two layers of Whatman grade 3 filter paper. As the table shows, each bacterial filter was unfailingly effective; no bacilli could be detected in any of the filtrates. Unfiltered control suspensions, on the other hand, always produced heavy growth. Double-layer filter paper did not sterilize, although growth from its filtrate was not as heavy as from unfiltered suspensions.

Since the significance of these results depends a great deal upon the capacity of the test medium to detect one bacillus passing through a filter, this ability was ascertained. A twenty-four hour culture of smegma bacilli in Kirchner medium with Tween® added to 0.05 per cent was diluted and the number of

TABLE 3

FILTRATION OF MYCOBACTERIUM SMEGMATIS FROM SATURATED HYDROCARBONS

Hydrocarbon	Filter	Number of 0.3 Ml. Samples	Number of Samples Showing Growth
Petroleum ether	Paper	10	10
	Glass	10	0
	Mandler	10	0
	Seitz	10	0
	MF	10	0
	None	2	2*
Petroleum ether	Mandler	2	0
	Seitz	2	0
	MF	2	0
	None	1	1
Pentane	Mandler	2	0
	Seitz	2	0
	MF	2	0
	None	1	1
Cyclohexane	Mandler	2	0
	Seitz	2	0
	MF	2	0
	None	1	1
Heptane	Mandler	2	0
	Seitz	2	0
	MF	2	0
	None	1	1

* Growth on all plates inoculated with unfiltered suspensions was abundant and confluent.

bacillary units were determined microscopically with a counting chamber. Further appropriate dilutions were made in sterile medium, and plate counts were set up. Microscopic and culture counts showed the original suspension to contain 1.23×10^7 and 2.44×10^7 bacterial units per ml., respectively. These figures agree closely, considering the unavoidable mechanical dispersal of bacterial clumps during dilution. The medium, therefore, seems sensitive enough to have detected single viable bacillary units had any eluded the filters. The possibility that the evaporation of one or more of the hydrocarbons from an inoculated plate was not as complete as it appeared to the eye and nose and that enough remained in or on the medium to lessen its sensitivity was eliminated by comparing numbers of bacilli developing on plates treated with each of the solvents. This was done in the filtration experiments, the bacilli developing upon plates not previously exposed to any solvent. The numbers of colonies counted on control and treated plates were practically the same.

Almost invariably tubercle bacillary extracts have been prepared by pro-

longed exposure of the bacilli to a solvent, a procedure which could so alter the physical properties of the bacilli that they could become able to pass through common filters. A culture method test of this hypothesis is limited by the length of time mycobacteria survive in the saturated hydrocarbons. The following experiments show that exposure for two or three days does not lead to contaminated filtrates.

Smegma bacilli were suspended in heptane, petroleum ether, and cyclohexane, exactly as in previous experiments, in aluminum foil-capped flasks. These flasks were kept at room temperature (about 26°C.) with occasional shaking for forty-eight hours and the suspensions then were filtered through Seitz, Mandler, and MF filters. Five 0.5 ml. samples of each filtrate were inoculated to glycerol-nutrient agar plates, as was done in previous tests.

It may be seen in table 4 that the large numbers of bacilli remaining viable after forty-eight hours' incubation in the various solvents were without exception completely removed by each filter. A similar test of smegma bacilli suspended in cyclohexane and sampled after three and six days at room temperature confirmed these findings for the three-day interval. Since no bacilli remained alive by the sixth day, however, testing could not encompass this interval. Most of the bacilli had died by the third day, but remaining viable bacilli did not pass through the filters.

Failure of these saprophytic mycobacteria suspended in saturated hydrocarbons to pass through bacteria-retaining filters encouraged similar experiments with virulent tubercle bacilli. H37Rv tubercle bacilli grown and suspended, as described above, at a 2.4 mg. per ml. concentration were filtered from heptane and from cyclohexane suspensions with Seitz, Mandler, and MF filters. The

TABLE 4

FILTRATION OF MYCOBACTERIUM SMEGMATIS FROM TWO-DAY SUSPENSIONS IN SATURATED HYDROCARBONS

Hydrocarbon	Filter	Number of 0.5 Ml. Samples	Number of Samples Showing Growth
Petroleum ether	Mandler	5	0
	Seitz	5	0
	MF	5	0
	None	2	2*
Cyclohexane	Mandler	5	0
	Seitz	5	0
	MF	5	0
	None	2	2†
Heptane	Mandler	5	0
	Seitz	5	0
	MF	5	0
	None	2	2*

* Heavy, confluent growth.

† Heavy growth.

procedure, with added precautions, was the same as that used with *M. smegmatis*; samplings were similarly made on Dubos oleic-acid–albumin agar, the ability of which to detect single viable units has been attested (12). It may be seen in table 5 that tubercle bacilli are filtered as effectively as smegma bacilli from these organic solvents.

In a like experiment, H37Ra tubercle bacilli suspended in heptane, cyclohexane, and petroleum ether were filtered through MF, Seitz, and Mandler filters, respectively. As table 6 shows, none of the 37 plates of either Dubos medium or International Union Against Tuberculosis (IUTM) egg medium (13) inoculated with organic solvent filtrates detected any bacilli, whereas all plates inoculated with unfiltered control suspensions showed very heavy, confluent mycobacterial growth.

TABLE 5

FILTRATION OF MYCOBACTERIUM TUBERCULOSIS VAR. HOMINIS (H37Rv) FROM SATURATED HYDROCARBONS

Hydrocarbon	Filter	Number of 0.5 Ml. Samples	Number of Samples Showing Growth*
Heptane	Mandler	7	0
	Seitz	7	0
	MF	7	0
	None	1	1†
Cyclohexane	Mandler	7	0
	Seitz	7	0
	MF	7	0
	None	1	1†

* On Dubos oleic-acid–albumin agar.

† Heavy, confluent growth.

TABLE 6

FILTRATION OF MYCOBACTERIUM TUBERCULOSIS VAR. HOMINIS (H37Ra) FROM SATURATED HYDROCARBONS

Hydrocarbon	Filter	Number of 0.5 Ml. Samples*	Number of Samples Showing Growth
Petroleum ether	Mandler	13	0
	None	2	2†
Cyclohexane	Seitz	12	0
	None	3	3
Heptane	MF	11	0
	None	2	2

* Number of samples made on both Dubos medium and International Union Against Tuberculosis egg medium plates.

† All unfiltered control plates showed heavy, confluent growth.

This experiment, in addition to the preceding ones, leaves no doubt that bacteria-retaining filters can remove tubercle bacilli effectively from organic solvents, for the excellent sensitivity of both Dubos medium and egg IUTM medium was confirmed by comparison of counts and cultures.

Discussion

Saturated hydrocarbons appear to be nearly as harmless for smegma and tubercle bacilli as distilled water. This has provided the means to prove bacterial filters capable of completely removing mycobacteria from organic solvents. Among the numerous experiments done, there is no single instance of media, known to be capable of detecting single mycobacterial units, disclosing any of these bacilli in filtrates from such filters. It remains possible that mycobacteria which are no longer viable because of physical changes wrought on them by prolonged exposure to a solvent may pass through filters because of these changes. Within the scope of the present technique, however, no tendency toward this has been observed.

Although only the saturated hydrocarbons were harmless enough for these experiments, their results probably apply to most other organic solvents because the majority are less polar than water, from which mycobacteria are easily filtered (1), and more polar than the saturated hydrocarbons. From this statement it follows that the degree of solvent polarity, important in some kinds of filtration, apparently has nothing to do with the filtration of mycobacteria from organic solvents. Perhaps in this instance filtration is purely mechanical. From statements by the Millipore Filter Corporation (14), this could seem definitely so of MF filters.

All of the filters tried except double-layer Whatman grade 3 filter paper[5] were effective, but not all were equally convenient. The UF fritted glass filter was quite difficult to clean and filtered very slowly; MF, Seitz, and Mandler filters worked faster. The Mandler filter was easily cleaned by forcing the solvent through it in reverse. Seitz pads and MF filter disks are disposable. Seitz and Mandler filters absorb a good deal of fluid and therefore are somewhat wasteful, but they can be used with most organic solvents. The MF filter, which absorbs virtually no fluid, is restricted to those which do not alter it. Fortunately for research in tuberculosis, most of the lipids extractable from tubercle bacilli which possess biologic activity are soluble in the saturated hydrocarbons. Thus, a total crude lipoidal extract can be dissolved in one of these, filtered through an MF filter for complete decontamination, and subsequently treated, fractionated, or stored as desired. The Mandler filter is more likely to be mechanically defective and thereby less reliable than either Seitz or MF filters.

That bacteriologic filters effectively remove bacilli from suspension, either

[5] Occasionally investigators have used tubercle bacillary lipids which apparently have been filtered only through filter paper to free them of bacilli (15, 16). Unfortunately, they have not described what kind of filter paper was used or how they employed it. Whatman grade 3 filter paper was used here because it is one of the finest grades commonly available in most laboratories.

organic solvent or aqueous, is not to say that they remove bacillary debris. Since this debris may be biologically active, unguarded conclusions about the biologic effects of filtered bacillary extracts must be avoided. The present experiments have shown only that a filtrate from extracted, but structurally intact, bacilli, produced under very carefully controlled conditions, will be free of intact bacilli, and that, therefore, biologic effects observed are not due to bacillary contamination. Although the unreliability of bacterial filters, used either improperly or with systems that have not been previously tested, has occasionally been pointed out (17, 18), unfortunately it is often not realized by those who employ them. It should be stated that the present studies cannot necessarily be used to predict the efficacy of bacterial filters in removing other genera of bacteria from organic solvents.

Note should be taken of the interesting fact that among the several organic solvents examined only the saturated hydrocarbons were relatively harmless for *M. smegmatis*. An exception was ligroin, which may owe its lethal effect to materials, such as permanganate, used in its purification. Saturated hydrocarbons harmless for smegma bacilli (pentane, cyclohexane, petroleum ether, and heptane) were no more harmful for the H37Rv and H37Ra strains of *M. tuberculosis*.

The remarkable bactericidal effect of *o*-dichlorobenzene vapor may be practical for decontamination without heat; however, this effect has not been investigated beyond a preliminary status.

Summary

Many of the biologic properties of lipoidal constituents extracted from tubercle bacilli have remained imperfectly understood, despite numerous experiments with them, because of the difficulty of separating them from the bacilli and, especially, of proving them uncontaminated. With the intent of testing by *in vitro* culture the efficacy of common bacteria-retaining filters in freeing organic solvents of mycobacteria, the lethal effects on *Mycobacterium smegmatis* of 18 commonly used organic solvents were tested. Most of the solvents killed these bacilli by contact in a short time, and *o*-dichlorobenzene in addition emanated a bactericidal vapor. Petroleum ether (30–60°C., boiling point), pentane, cyclohexane, and *n*-heptane proved no more lethal over a period of two days at room temperature than distilled water.

Heavy suspensions of smegma bacilli in each of these indifferent saturated hydrocarbons were completely cleared of bacilli by filtration through either fritted glass, Seitz, or Mandler filters (all of bacteria-retaining grade) and through MF (Millipore Corporation) filters, but not through a double layer of Whatman grade 3 filter paper. Similar suspensions of human tubercle bacilli, both strains H37Rv and H37Ra, likewise were unfailingly cleared by Seitz, Mandler and MF filters; fritted glass and filter-paper filters were not tried with these strains. Filtrates were cultured on media known or shown able to detect single, viable bacillary units such as might have escaped filtration.

Sumario

Filtración de Micobacterias de Solventes Orgánicos

A pesar de numerosos experimentos, continúan entendiéndose imperfectamente muchas de las propiedades biológicas de los componentes lipoidales extraídos de los bacilos tuberculosos, debido a lo difícil que es separarlos de los bacilos y demostrar que no están contaminados. Con la intención de comprobar con cultivos *in vitro* la eficacia de los filtros corrientes de retención de bacterias para desembarazar de micobacterias a los solventes orgánicos, se comprobaron los efectos letales ejercidos sobre el *Mycobacterium smegmatis* por 18 solventes orgánicos de uso corriente. La mayoría de los solventes mató a dichos bacilos por contacto en poco tiempo y el *o*-diclorobenceno emitió además un vapor bactericida. El éter de petróleo (punto de ebullición, 30° a 60°C.), el pentano, el ciclohexano y el *n*-heptano no resultaron ser más letales que el agua destilada durante un período de dos días a la temperatura ambiente.

Suspensiones espesas del bacilo del esmegma en cada uno de esos inertes hidrocarburos saturados quedaron completamente desembarazadas de bacilos por la filtración a través de filtros ya de vidrio fundido, de Seitz o de Mandler (todos de capacidad retentora de bacterias) y a través de filtros MF, pero no a través de una doble capa del papel-filtro de Whatman de grado 3. Suspensiones semejantes de bacilos tuberculosos humanos, cepas H37Rv y H37Ra, fueron también desembarazadas invariablemente de bacterias por los filtros de Seitz, Mandler y MF; no se probaron los filtros de vidrio fundido y de papel-filtro con estas cepas. Los filtrados fueron cultivados en medios que se sabía o que se demonstró que podían descubrir unidades bacilares viables y aisladas, de las que hubieran podido evadir la filtración.

Resume

Filtration des bactéries à partir de solvants organiques

De nombreuses propriétés biologiques des constituants lipoïdes extraits du bacille de Koch demeurent imparfaitement comprises, à cause de la difficulté à les extraire des bacilles et surtout de démontrer qu'ils ne sont pas contaminés. En essayant de tester par la culture *in vitro* l'efficacité des filtres retenant les bactéries ordinaires à libérer les solvants organiques des mycobactéries, l'action léthale exercée par 18 solvants d'usage commun sur le *M. smegmatis* a été testée. La plupart des solvants tuaient rapidement ces bacilles par contact; en outre, il émanait du *o*-diochlorobenzène une vapeur bactéricide. L'ether de pétrole (point d'ébullition 30–60°), le pentane, le cyclohexane et le n-heptane conservés à la température ambiante pendant deux jours n'avait pas plus d'action léthale que l'eau distillée.

Les suspensions denses de *M. smegmatis* dans chacun de ces hydrates de carbone saturés indifférents étaient complètement débarrassées de bacilles par filtration sur verre fritté, ou sur filtres Seitz ou Mandler (tous capables de retenir les bacteries) et sur filtres MF (Millipore Corporation), mais ne l'étaient pas lorsque le filtre était constitué par une double couche de papier filtre Whatman No. 3. Des suspensions semblables de bacilles humains furent cultivées sur des milieux connus ou démontrés aptes à déceler les unités bacillaires pouvant avoir échappé à la filtration.

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THE EFFECT OF THIOCARBANIDIN AND RELATED COMPOUNDS ON MYCOBACTERIUM TUBERCULOSIS VAR. HOMINIS IN VITRO AND IN VIVO[1]

GUY P. YOUMANS, ANNE S. YOUMANS, AND LEONARD DOUB

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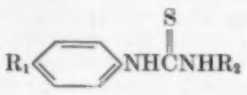
INTRODUCTION

The antituberculous activity of the thioureas became evident in the screening program of the writers with the demonstration that compounds conforming to formula Ia, where R_1 is a highly electronegative group, possessed appreciable capacity to suppress an experimental tuberculous infection of mice. Continuation of this work led to the finding that certain thiocarbanilides, thioureas of type formula Ib, were much more effective.

I. 

a; Phenylalkylthioureas
R_2 = alkyl
b; Thiocarbanilides
R_2 = substituted phenyl

Several hundred thioureas were prepared and tested during the course of this work. A detailed study of the relationship of structure to tuberculostatic activity in this large group of compounds will be published elsewhere (1). In this paper the degree and kind of activity exhibited by 4-(α-pyridyl)-4′-isobutoxy thiocarbanilide (thiocarbanidin[2]), the clinically most promising compound, and other representative thioureas will be presented, with emphasis on some of the more active thiocarbanilides.

During the progress of this research, papers appeared announcing the antituberculous activity of other types of thiocarbanilides (2–5). Preliminary observations on the antituberculous activity in human beings of two of these thiocarbanilides indicated that in doses of 3 to 6 gm. per day they were less effective than streptomycin, but more effective than *p*-aminosalicylic acid (PAS) (6, 7). Buu-Hoï and associates (8, 9) also have reported on the *in vitro* bacteriostatic activity of a variety of thiocarbanilide compounds.

METHODS

The methods employed for the evaluation of the antituberculous activity of drugs both *in vitro* and *in vivo* have been given in detail elsewhere (10–12). In brief, however, the methods were as follows:

In vitro tests: Modified Proskauer and Beck medium was used for all *in vitro* work. Compounds soluble in water were dissolved directly in this synthetic medium. The more insoluble compounds were first dissolved with 1.0 or 2.0 ml. of ethyl alcohol, acetone, ether, propylene glycol, 0.1 molar sodium hydroxide, or 0.1 molar hydrochloric acid, depending

[1] From the Department of Microbiology, Northwestern University Medical School, Chicago, Illinois; and the Research Laboratories, Parke, Davis & Company, Detroit, Michigan.

[2] Supplied as Thioban by Parke, Davis & Company, Detroit, Michigan, and identified also as Y-9525.

upon their solubility in these substances. The solutions were then diluted with medium to make a concentration of 10 mg. per 100 ml. If difficulty was experienced in dissolving a heat-stable substance, it was heated to boiling for five minutes, and the subsequent dilutions were made while the solution was still warm. Those few compounds which would not go completely into solution in any manner at this concentration were filtered to remove any undissolved material, and an estimate was made of the amount which did not go into solution. Ten different concentrations of each drug were prepared from the 10 mg. per 100 ml. concentration by serial dilution in the medium, each concentration representing one half of the preceding one. The heat-stable compounds were diluted and sterilized in the autoclave at 15 pounds of pressure for twenty minutes. Solutions of heat-labile compounds were filtered through either Berkefeld, sintered glass, or Swinney syringe-type filters, following which they were diluted aseptically in sterile Proskauer and Beck medium. Similar bacteriostatic tests were conducted in the medium, to which had been added sufficient sterile beef serum to make a final concentration of 10.0 per cent.

Each tube of each drug dilution and appropriate control was inoculated with approximately 0.1 mg. wet weight of a fine suspension of the virulent H37Rv strain of *M. tuberculosis* var. *hominis*. The suspension was prepared by grinding by hand with a sterile pestle in a sterile mortar a portion of a surface pellicle culture which had grown on the Proskauer and Beck medium for fourteen to twenty-one days. During the grinding process the culture was diluted gradually with 0.01 molar phosphate buffer solution (pH 7.0) until a fairly heavy suspension was obtained. This was then transferred to a sterile test tube and allowed to stand at room temperature for thirty minutes. At the end of this time the larger clumps had settled out, leaving a relatively fine homogenous supernatant suspension. This supernatant was transferred by decantation to a second sterile tube and standardized by the centrifugation of a 1.0 ml. aliquot in a Hopkins vaccine centrifuge tube for twenty minutes at 1,000 r.p.m. Following standardization the suspension was diluted with 0.01 molar phosphate buffer solution so that the inoculum for each tube would contain 0.1 mg. of tubercle bacilli.

Incubation was carried out at 37°C. in an air incubator. At the end of fourteen days of incubation the tubes were examined and the bacteriostatic activity of each compound was recorded as the least amount of drug which completely prevented the growth of the tubercle bacilli.

Mouse strain and test organism: White mice of the "Strong A" strain weighing between 18 and 22 gm. were employed. These mice were infected intravenously by injection into one of the lateral tail veins of 1.0 mg., wet weight, of the virulent H37Rv strain of *Mycobacterium tuberculosis* var. *hominis*. Suspensions of this microorganism for injection into the mice were prepared and standardized in the same manner as the suspensions employed for the *in vitro* tests. For routine experiments 10 mice were employed for each drug concentration. Larger numbers of mice and replicate tests were frequently employed to determine more accurately the actual effect on the tuberculous infection or to determine the reality of equivocal findings. Mice infected with tubercle bacilli, but which received no treatment, were used as controls in all experiments.

Administration of drugs: Except in the case of the one compound indicated in the table, all compounds were administered to the mice by the drug diet method. Rockland standard mouse ration pellets were ground to fine powder. The desired concentrations of each drug were added to the powdered mouse ration and mixed by prolonged shaking. One day before the mice were to be infected with tubercle bacilli, this powdered ration containing the drug was substituted for the standard mouse ration pellets.

The one drug that was administered intraperitoneally and subcutaneously was given in two injections each day, approximately eight hours apart.

Evaluation of results: Following administration of the drugs for fourteen days, the mice were returned to a normal diet and a record was kept of the time of death in days of these animals as well as the time of death of the control animals which received no drug. When all of the mice had succumbed, the cumulative percentage of mice dead in each group was plotted on logarithmic probability paper against the time of death in days. From the straight line so obtained the median survival (St_m) was estimated. The significance of

differences between the median survival time of control and treated groups of mice, or between treated groups of mice, was calculated using the method recommended by Litchfield (13). The delta median survival time given in table 1 (ΔSt_m) represents a statistically significant increase in median survival time of the mice treated with a given drug over the median survival time of the control. The median survival times of the controls ranged between 11.0 and 19.5 days. Where it is indicated that more than 20 mice were used for the evaluation of a compound, the ΔSt_m represents the difference between the mean of the median survival time determinations of several drug diet experiments and the mean of the median survival times of groups of homologous control mice.

Results

The results of both *in vitro* and *in vivo* tests for antituberculous activity of 24 representative thioureas are given in table 1. The first seven compounds are examples of phenylalkylthioureas and are representative of compounds conforming to the formula Ia given in the introduction, where R_1 is a highly electronegative group and R_2 is an alkyl group.

The *in vitro* bacteriostatic activities of these compounds were low and seemed to be little affected by the presence of serum in the medium.

Appreciable activity was noted *in vivo*, but only when high concentrations were employed in the diet, 0.25 to 4.0 per cent. There was relatively little difference, however, in the survival time of the mice and, therefore, of the *in vivo* effectiveness of the drugs within this dosage range.

The remaining 17 compounds are examples of thiocarbanilides of an entirely different type which conform to the formula Ib given in the Introduction. For activity in this class, R_1 is preferably alkoxy.

The *in vitro* activity of the thiocarbanilides was very much greater than that of the phenylalkylthioureas. The activity in the modified Proskauer and Beck medium of many of these compounds was of a high order. Upon incorporation of serum into the medium, however, the *in vitro* bacteriostatic activity was reduced to approximately the same level as that obtained with the phenylalkylthioureas.

The activity of the thiocarbanilides *in vivo* was also appreciably greater than that of the phenylalkylthioureas, since they produced a significant prolongation of the median survival time of the tuberculous mice at a very much lower drug diet concentration. Some of these thiocarbanilides showed a significant degree of activity at drug diet concentrations as low as 0.004 or 0.008 per cent. This would correspond to a drug intake of between 10 and 20 mg. per kg. per day.

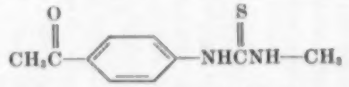
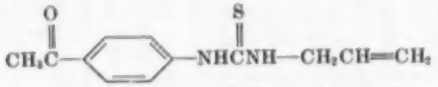
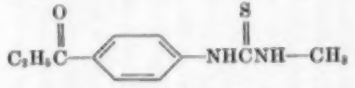
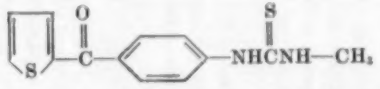
The one thiourea which was administered parenterally, No. 1, showed no suppressive effect on the tuberculous infection of mice although the compound in a comparable dose was effective when given by the oral route. The reason for this discrepancy is unknown.

Discussion

The chemotherapeutic activity of the thiocarbanilides reported upon in this paper is rather unique because, although these compounds at very low dosage suppress an acute experimental tuberculous infection in the mouse, the therapeutic activity does not increase markedly with large increases in drug intake. These compounds at low doses increase the median survival time in mice to the

TABLE 1

THE EFFECT OF TWENTY-FOUR REPRESENTATIVE THIOUREA COMPOUNDS ON MYOCBACTERIUM TUBERCULOSIS VAR. HOMINIS IN VITRO AND IN VIVO

Number	Compound	*In Vitro*		*In Vivo*			
		Minimal Growth Inhibiting Concentration in Mg. per 100 Ml.		Mode of Administration and Amount Administered		Number of Mice	ΔSt_{20}
		Proskauer and Beck Medium	Proskauer and Beck Medium plus 10.0 Per Cent Bovine Serum	Drug diet Concentration in Per Cent	Mg/Kg/ Day Given Parenterally		
1	 1(*p*-acetylphenyl)-3-methyl-2-thiourea	5.000	2.500	1.000		10	19.50
				0.500		172	17.10
				0.250		19	11.50
				0.125		9	4.00
					1,250.0*	10	toxic
					250.0*	9	0.00
					500.0†	8	toxic
					250.0†	9	0.00
					125.0†	10	0.00
2	 1-(*p*-acetylphenyl)-3-allyl-2-thiourea	5.000	10.000	1.000		10	toxic
				0.500		10	14.00
3	 1-(*p*-propionylphenyl)-3-methyl-2-thiourea	5.000	10.000	1.000		10	16.00
4	 1-[*p*-(2-thenoyl)phenyl]-3-methyl-2-thiourea	0.600	5.000	4.000		5	17.00
				2.000		10	18.00
				1.000		20	23.70
				0.500		20	6.25

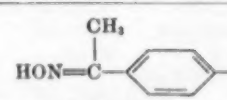
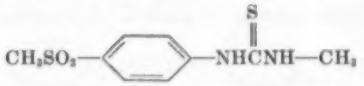
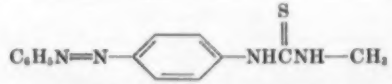
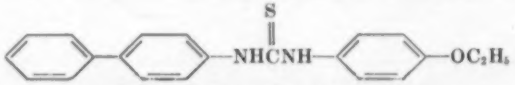
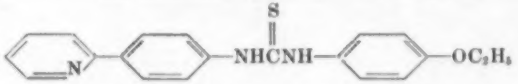
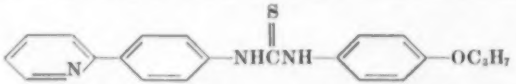
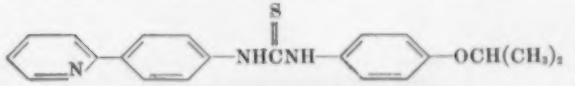
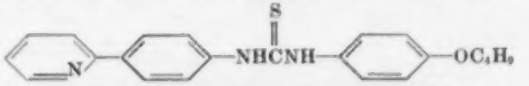
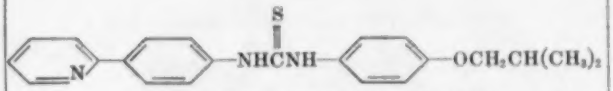
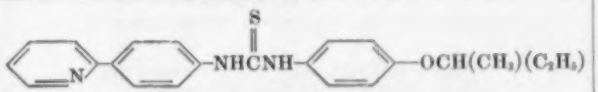
5	 1-[*p*-(1-oximidoethyl)phenyl]-3-methyl-2-thiourea	0.156	0.156	1.000 0.500 0.250 0.062		7 38 20 9	15.00 23.00 20.00 4.00
6	 1-(*p*-methylsulfonylphenyl)-3-methyl-2-thiourea	>10.000	>10.000	0.500		20	9.00
7	 1-(*p*-phenylazophenyl)-3-methyl-2-thiourea	10.000	10.000	0.500		9	3.00
8	 4-phenyl-4′-ethoxy thiocarbanilide	0.039	>10.000	0.500 0.030		9 10	17.50 4.00
9	 4-(α-pyridyl)-4′-ethoxy thiocarbanilide	0.039	10.000	0.250 0.125 0.060 0.030		19 34 29 30	32.00 30.50 27.00 9.00
10	 4-(α-pyridyl)-4′-propoxy thiocarbanilide	0.156	>10.000	0.125 0.030 0.008 0.004		10 10 10 10	22.50 22.50 18.50 0.00

TABLE 1-*Continued*

Number	Compound	*In Vitro*		*In Vivo*			
		Minimal Growth Inhibiting Concentration in Mg. per 100 Ml.		Mode of Administration and Amount Administered		Number of Mice	ΔSt_{10}
		Proskauer and Beck Medium	Proskauer and Beck Medium plus 10.0 Per Cent Bovine Serum	Drug Diet Concentration in Per Cent	Mg/Kg/ Day Given Parenterally		
11	 4-(α-pyridyl)-4′-isopropoxy thiocarbanilide	0.078	5.000	0.125 0.030		10 10	24.50 6.50
12	 4-(α-pyridyl)-4-butoxy thiocarbanilide	0.019	10.000	0.250 0.030 0.016 0.008 0.004		10 19 20 30 20	22.00 22.50 14.50 14.50 0.00
13	thiocarbanidin  4-(α-pyridyl)-4-isobutoxy thiocarbanilide	0.078	10.000	0.125 0.030 0.016 0.008 0.004 0.002		8 9 20 10 10 20	22.50 20.50 14.50 16.00 4.00 0.00
14	 4-(α-pyridyl)-4′-sec-butoxy thiocarbanilide	0.156	5.000	0.032 0.008 0.004		10 10 9	18.50 0.00 0.00

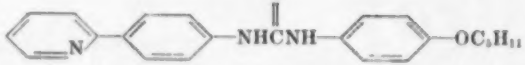
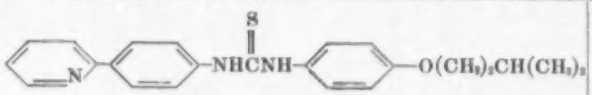
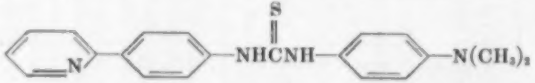
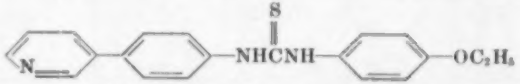
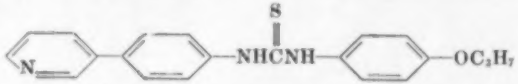
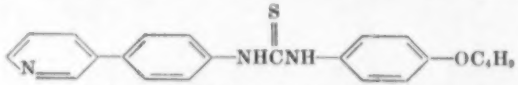
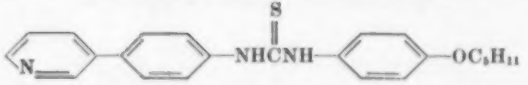
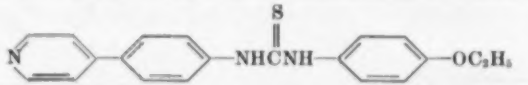
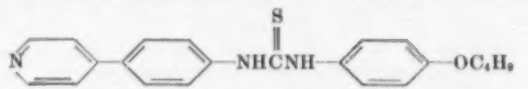
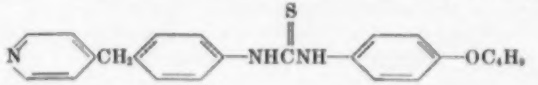
15	 4-(α-pyridyl)-4-amoxy thiocarbanilide	0.078	10.000	0.125 0.030 0.008 0.004		9 10 10 10	26.50 24.50 0.00 0.00
16	 4-(α-pyridyl)-4-isoamoxy thiocarbanilide	0.078	1.250	0.125 0.030 0.008 0.004		10 10 10 10	15.50 13.50 0.00 0.00
17	 4-(α-pyridyl)-4′-dimethylamino thiocarbanilide	0.078	>10.000	0.125 0.030		10 10	8.50 6.50
18	 4-(β-pyridyl)-4′-ethoxy thiocarbanilide	0.039	>10.000	0.250 0.030 0.015 0.008		9 18 8 8	28.50 26.00 9.00 5.00
19	 4-(β-pyridyl)-4′-propoxy thiocarbanilide	0.156	10.000	0.250 0.016 0.004		10 9 10	25.50 11.50 0.00
20	 4-(β-pyridyl)-4′-butoxy thiocarbanilide			0.125 0.016 0.004		10 10 10	18.50 5.50 0.00

TABLE 1—*Concluded*

Number	Compound	*In Vitro*		*In Vivo*			
		Minimal Growth Inhibiting Concentration in Mg. per 100 Ml.		Mode of Administration and Amount Administered		Number of Mice	ΔSt_{50}
		Proskauer and Beck Medium	Proskauer and Beck Medium plus 10.0 Per Cent Bovine Serum	Drug Diet Concentration in Per Cent	Mg/Kg/ Day Given Parenterally		
21	 4-(β-pyridyl)-4′-amoxy thiocarbanilide	0.078	10.000	0.100 0.015		10 10	25.00 3.50
22	 4-(γ-pyridyl)-4′-ethoxy thiocarbanilide	0.039	10.000	0.250 0.030		10 10	21.00 13.50
23	 4-(γ-pyridyl)-4′-butoxy thiocarbanilide	0.019	5.000	0.250 0.016 0.004		10 10 9	25.50 12.50 0.00
24	 4-(γ-pyridylmethyl)-4′-butoxy thiocarbanilide	0.019	10.000	0.100 0.030		10 10	15.00 0.00

* Subcutaneously
† Intraperitoneally

same extent as that observed with the largest doses of para-aminosalicylic acid. At very low doses these thiocarbanilides also increase the median survival time to about the same extent as comparable doses of isoniazid or streptomycin. However, at somewhat higher dosage levels the activity shown by isoniazid and streptomycin is much greater. These results seem to indicate that these thiocarbanilides should be compared with para-aminosalicylic acid. It is possible that the thiocarbanilides might be used advantageously instead of PAS in association with isoniazid or streptomycin in the therapy of tuberculosis in humans. A strict extrapolation of these results would lead one to expect that less than 1 gm. of one of the thiocarbanilides could be substituted for the approximately 12 gm. of PAS presently administered in combined therapy.

Because of its activity and certain favorable pharmacologic properties[3] which will be reported upon in detail elsewhere, thiocarbanidin has been selected for clinical trial. The final decision upon the place of this new thiocarbanilide in the chemotherapy of tuberculosis in human beings will of necessity have to await the outcome of clinical studies which now are in progress.

Summary

The antituberculous activity of 24 new thiourea compounds has been given. Seven of these compounds were phenylalkylthioureas and 17 were thiocarbanilides.

The thiocarbanilides were found to be more active *in vitro* and *in vivo* than were the phenylalkylthioureas. The maximal effectiveness of the thiocarbanilides for the suppression of an experimental tuberculous infection in mice was found to be about equal to the effectiveness of para-aminosalicylic acid. The thiocarbanilides, however, showed this activity at very much lower drug diet concentrations than did PAS.

The significance of these findings has been discussed and it was suggested that the greatest usefulness of thiocarbanidin, the most promising thiocarbanilide, might prove to be as a substitute for PAS in association with streptomycin or isoniazid for the treatment of tuberculosis.

Sumario

El Efecto de la Tiocarbanidina y los Compuestos Afines sobre el Mycobacterium Tuberculosis var. Hominis in Vitro e in Vivo

Se describe la actividad antituberculosa de 24 nuevos compuestos de la tiourea. Siete de esos compuestos eran fenilalquiltioureas y 17 tiocarbanilidas.

Las tiocarbanilidas resultaron ser *in vitro* e *in vivo* más activas que las fenilalquiltioureas. La eficacia máxima de las tiocarbanilidas para la supresión de una infección tuberculosa experimental en los ratones resultó ser aproximadamente igual a la del ácido para-aminosalicílico. Sin embargo, las tiocarbanilidas mostraron esa actividad a concentraciones mucho menores en la alimentación que el ácido para-aminosalicílico.

Se sugiere que la mayor utilidad de la tiocarbanidina, la tiocarbanilida que más promete, tal vez sea como substituto del ácido para-aminosalicílico en combinación con la estreptomicina o la isoniacida para el tratamiento de la tuberculosis.

[3] A microbiologic determination of the concentration of antituberculous substances in the blood after the administration of several of the most active thiocarbanilides to monkeys revealed significant blood concentrations only for the isobutoxy thiocarbanilide.

Resume

L'action de la thiocarbanidine et de composés apparentés sur le Mycobacterium tuberclosis var. hominis in vitro et in vivo

L'activité antituberculeuse de 24 nouveaux composés thioureïdes est mentionnée. Sept de ces composés étaient ces phénylalkylthiouréides et 17 des thiocarbanilides.

Les thiocarbanilides se révèlèrent plus actives *in vitro* et *in vivo* que les phénylalkythiouréides. L'efficacité maxima des thiocarbanilides à inhiber l'infection expérimentale chez la souris a été trouvée à peu près égale à l'efficacité de l'acide para-aminosalicylique. Cependant, les thiocarbanilides incorporées à la ration à une concentration beaucoup plus réduite, possédaient la même activité que l'acide para-aminosalicylique (PAS).

L'article suggére qu'en raison des avantages pratiques qu'elle offre la thiocarbanilide, composé plein de promesses, pourrait remplacer le PAS dans l'association à la streptomycine ou à l'isoniazide dans le traitement de la tuberculose.

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REFUSAL OF SURGERY AMONG TUBERCULOUS PATIENTS[1]

GEORGE CALDEN, JOHN R. THURSTON, AND WILLIAM C. LEWIS

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INTRODUCTION

During the past decade, surgical excision of tuberculous lung tissue has achieved noteworthy success. Despite the efficacy of this procedure, however, all too often the patient turns down his physician's recommendation and refuses to submit to surgery. Although in many respects such surgery is elective, the patient's unwillingness to undergo the operation can be regarded as a serious impediment to a fuller and more rapid recovery. One cannot generalize on the medical consequences of the refusal of surgery in each individual case. In terms of the attainment of optimal treatment, however, the behavior of the person who refuses surgery in many instances can be placed in the same category as that of the patient who pours his medication down the drain, violates his bed-rest restrictions, or disrupts treatment by walking out of the hospital against medical advice.

The majority of patients hospitalized for tuberculosis become fairly familiar and conversant with the various aspects of their disease and treatment program. Presumably, a procedure like surgical resection, which physically removes a substantial portion of pulmonary disease and assures the patients of a greater chance of an enduring recovery, would be readily accepted by them. Unfortunately, this has not been borne out by experience. In most tuberculosis hospitals there continues to exist a sizable segment of the patient population that refuses to be operated upon "no matter what."

The aim of the present study is to explore several of the factors which may have relevance to surgery refusal. This investigation is a preliminary one dealing with the pertinent medical and demographic variables that may be linked to the problem. In subsequent studies, the writers plan to investigate the psychological and the interpersonal, patient-staff factors which bear upon the patient's decision to reject pulmonary surgery.

Although there have been a considerable number of studies dealing with the management of tuberculous patients who obstruct treatment (particularly those who leave the hospital prematurely), there has been a dearth of inquiry into the specific problems of refusal of surgery. Related to the present study, however, are several articles which review the psychological problems encountered by patients facing pulmonary surgery (1–3). The writers discuss the conscious fears and the unconscious resistances which patients have to accepting surgery. They also stress the advisability for staff personnel (the physician, surgeon, anesthetist, or social worker) to deal with the psychological as well as the organic aspects of surgical treatment.

[1] From the Psychology Service and Psychosomatic Department of the Veterans Administration Hospital, Madison, Wisconsin.

Materials and Method

From the day on which the Veterans Administration Hospital in Madison, Wisconsin, opened in September, 1951, through 1956, the surgery board has recommended chest surgery for 1,005 tuberculous patients. The recommended surgical procedures consisted predominantly of resectional excisions of lung tissue on one or both sides. A small minority of operations involved pulmonary decortications and exploratory thoracotomies. Of the 1,005 patients, 814 accepted and underwent unilateral or bilateral surgery. In contrast, 191 patients refused to be operated upon. The surgery refusals customarily occurred after the hospital's surgery board had discussed the patients' case and had recommended surgical intervention. In a small number of cases, the ward physician notified the surgery board, in advance of a recommendation of the board, that the patient would not submit to surgery. These patients also were categorized as patients who refused surgery if the surgery board believed that surgery was indicated.

The materials used in this study are the medical and surgical records of the 191 patients who refused pulmonary surgery and the records of a representative sample of 191 patients (of the total 814) who accepted surgery (surgical group). Since the ratio of accepters is approximately four to one, the 191 subjects constituting the surgical group were selected by picking every fourth patient from the chronologic list of pulmonary surgery cases. Not only was the total number of subjects in the surgical group equal to the group which refused surgery but, in addition, the number of accepters were selected to match the number of those who refused surgery for each year. For example, there were 48 who refused surgery in 1954. Consequently, exactly 48 of the 183 patients who accepted surgery in 1954 were selected in order to equal the number of those who refused.

Data pertaining to age, race, medical condition, et cetera, were collected from each subject's hospital record. The significance of differences between the two groups in regard to each of the factors was determined statistically by using the chi-square test.

Results

Extent of the Problem of Refusal of Surgery

As indicated above, 191 of the 1,005 patients who were recommended for chest surgery refused to submit to the operation. The over-all surgery refusal rate, therefore, is *19 per cent*. An inspection of the data in table 1 indicates that, despite fluctuations from year to year, the surgery refusal rate has remained relatively constant. Approximately one of 5 patients turns down surgery.

TABLE 1

Annual Rates of Refusal of Surgery

Year	Patients Who Accepted Surgery	Patients Who Refused Surgery	Refusal Rates
			per cent
1951	4	1	20
1952	141	25	15
1953	160	29	15
1954	183	48	20
1955	182	55	23
1956	135	33	20
Totals	814	191	Mean 19

Medical Status

Extent of lesion: As shown in table 2, the patients who refused surgery did not differ significantly from those who accepted it in the extent of their tuberculosis. The data in this table are based on the diagnosis established by the medical therapy Board shortly after the patient's admission to the hospital.

Unilateral or bilateral nature of disease: Comparisons between the two groups of patients on the basis of whether their tuberculous disease was unilateral or bilateral also revealed no significant differences.

State of infectivity of sputum: The percentage of the patients who refused surgery whose culture (sputum and/or gastric) was negative for tubercle bacilli at the time of review by the surgery board was not substantially different from the percentage among those who accepted surgery.

Number of sides recommended for surgery: A comparison of the number of sides recommended for thoracic surgery revealed an absence of meaningful differences between the two groups. Analysis of table 2 indicates that the surgery board recommended as many one-sided or two-sided operations for the group which refused surgery as was done for the surgical group.

Chemotherapy, original or re-treatment: Data dealing with the patient's chemotherapy treatment background and extent of resectional surgery were not readily

TABLE 2

COMPARISON OF MEDICAL STATUS BETWEEN PATIENTS WHO ACCEPTED AND THOSE WHO REFUSED SURGERY

Medical Status	Patients Who Accepted Surgery	Patients Who Refused Surgery	Statistical Significance
Extent of lesion			
Minimal tuberculosis	29	26	
Moderate tuberculosis	70	77	
Far advanced tuberculosis	86	83	Chi-square = 0.64
Other	6	5	Not significant
Unilateral or bilateral nature of disease			
Unilateral involvement	63	62	Chi-square = 0.00
Bilateral involvement	128	129	Not significant
State of infectivity of sputum			
Negative culture	148	153	Chi-square = 0.25
Positive culture	43	38	Not significant
Number of sides recommended for surgery			
One side	147	148	Chi-square = 0.00
Two sides	44	43	Not significant
Chemotherapy: original treatment or re-treatment			
Original treatment	51	49	Chi-square = 0.03
Re-treatment	24	26	Not significant
Extent of resection			
Maximal	49	50	Chi-square = 0.00
Major focus	26	25	Not significant

available for subjects in the surgical group and the group which refused surgery during the years 1951–1953. In order to obtain a representative sample of those who refused surgery, 75 such patients, for whom these data were obtained during 1954–1956 were selected on a random basis. Seventy-five who were recommended for surgery in 1954–1956 and who accepted were selected in a similar fashion. A patient was placed in the original treatment category if his antimicrobial therapy program followed an uninterrupted course up to the time of surgery recommendation. The re-treatment cases consisted of those patients whose initial chemotherapy treatment was interrupted for any reason whatsoever for a period of two weeks or more.

As shown in table 2, those who refused surgery did not differ significantly from those who accepted it on the basis of original or re-treatment aspects of chemotherapy.

Extent of resectional surgery: Patients who were considered for surgery also were rated by the surgery board on the basis of extent of the resection. If the contemplated extent of surgery was maximal in nature aimed at "curing" the patient, he was categorized as belonging in the "maximal resection" group. If, on the other hand, the primary goal of surgery was to remove the major focus of infection (such as a huge cavity or a destroyed lobe) for purposes of "stabilizing" the patient's condition, his surgery was rated as a "major focus" resection. After surgery, this type of patient still would have considerable palpable disease left in either the remaining or the contralateral lung.

The results, as revealed in table 2, indicate that there were as many maximal and major focus resectional patients in the group which refused surgery as there were in the group which accepted it.

Demographic Factors

Age: There is a seven-year age difference between the two groups. The mean age of the group which refused is 43.3 years, whereas the mean age of the surgical group is 36.5 years. A comparison of the age ranges of the two groups, shown in table 3, reveals that patients in the 20- to 29-year age level are much more inclined to accept recommended surgery, whereas patients in the 50 to 59 and 60

TABLE 3

COMPARISON OF AGE BETWEEN PATIENTS WHO ACCEPTED SURGERY AND PATIENTS WHO REFUSED SURGERY

Age Ranges	Patients Who Accepted Surgery	Patients Who Refused Surgery
20–29	62	25
30–39	61	64
40–49	45	44
50–59	15	33
60–70	8	25
Mean age	36.4	43.3

Chi-square = 31.28; $P < 0.001$.

to 70 age ranges are more inclined to refuse. No significant differences appear among patients in the 30- to 50-year categories.

Race: The racial factor by itself appears to have little or no bearing upon surgery refusal or acceptance. Approximately the same ratio of Negro to white patients exists in each of the two surgery groups.

Marital status: Although the statistical differences between the two groups is of borderline significance, a trend does appear in comparing the two groups on the basis of marital status. Married patients seem slightly more inclined to accept surgery, whereas single, widowed, and divorced patients tend to refuse surgery more readily.

Occupation: The two groups differ significantly on the basis of occupational background. Inspection of the data (table 6) shows that patients in the surgical group are more likely to have had positions at the professional and managerial levels and to come from student ranks. In contrast, those who refuse surgery are more likely to be unskilled laborers. No meaningful differences appear between groups for the sales-clerical, skilled, and semi-skilled worker and farmer categories.

Service-connection: The status of the patient's military disability (whether service-connected or nonservice-connected) appears to have a bearing on whether he accepts or refuses surgery. As indicated in table 7, the surgical patient is more likely to have a service-connected tuberculous disability and to receive compensation for it than does the one who refuses surgery.

Hospital discharge status: A comparison of the type of discharge obtained by the two groups (table 8) reveals that the surgical patient is more apt to continue

TABLE 4

COMPARISON OF RACE BETWEEN PATIENTS WHO ACCEPTED SURGERY AND PATIENTS WHO REFUSED SURGERY

Race	Patients Who Accepted Surgery	Patients Who Refused Surgery
White	143	149
Negro	43	39
Other	5	3

Chi-square = 0.81; not significant.

TABLE 5

COMPARISON OF MARITAL STATUS BETWEEN PATIENTS WHO ACCEPTED SURGERY AND PATIENTS WHO REFUSED SURGERY

Marital Status	Patients Who Accepted Surgery	Patients Who Refused Surgery
Married	86	67
Single	56	64
Separated	19	13
Divorced	26	36
Widowed	4	11

Chi-square = 8.90; $P < 0.07$; borderline significance.

TABLE 6

COMPARISON OF OCCUPATIONAL STATUS BETWEEN PATIENTS WHO ACCEPTED SURGERY AND PATIENTS WHO REFUSED SURGERY

Occupation	Patients Who Accepted Surgery	Patients Who Refused Surgery
Professional	13	9
Managerial	11	3
Sales-clerical	15	18
Skilled workers	38	34
Semi-skilled workers	61	58
Unskilled laborers	38	60
Farmers	5	7
Students	10	2

Chi-square = 16.25; $P < 0.05$.

TABLE 7

COMPARISON OF MILITARY SERVICE-CONNECTION BETWEEN PATIENTS WHO ACCEPTED SURGERY AND PATIENTS WHO REFUSED SURGERY

Service Connection	Patients Who Accepted Surgery	Patients Who Refused Surgery
Service-connected	70	51
Nonservice-connected	121	140

Chi-square = 3.92; $P < 0.05$.

TABLE 8

COMPARISON OF HOSPITAL DISCHARGE STATUS BETWEEN PATIENTS WHO ACCEPTED SURGERY AND PATIENTS WHO REFUSED SURGERY

Discharge	Patients Who Accepted Surgery	Patients Who Refused Surgery
Maximal hospital benefit	117	79
Unsanctioned discharge	54	75
Transfer	10	20
Still in hospital	9	16
Death	1	1

Chi-square = 9.22; $P < 0.01$.

his hospitalization until he has received a regular, maximal hospital benefit discharge, than the one who refuses surgery. The one who refuses is more likely to leave the hospital prematurely or to obtain a transfer to another sanatorium.

DISCUSSION

From the results of this study, it appears that the tuberculous patient who refuses pulmonary surgery can be distinguished from the surgical patient on the basis of several factors. The patient most likely to turn down surgery tends to be more than fifty years of age, is probably unmarried, does not draw compensation for military service-connected tuberculosis, and is apt to be an unskilled

laborer. The patient most inclined to accept surgery is in the twenty-year-old age range, is currently married, has obtained a service-connected disability compensation for tuberculosis, and has been employed in positions involving professional or managerial duties, or he has been a student prior to hospital admission. In addition, the patient who refuses surgery tends to disrupt his hospitalization by leaving irregularly or by receiving a transfer more readily than the surgical patient. The patient's medical condition by itself, i.e., the extent of his tuberculosis, the unilateral or bilateral nature of his disease, the degree of infectiousness of his sputum, the number of sides recommended for surgery, the extent of recommended resection, and the patient's chemotherapy treatment background, does not differentiate the two groups. The patient's race also does not appear to be a significant factor.

Judging from the tables presented above, the age difference probably is the most significant single discriminator between the two groups. It is also likely that the factor of age contributes to the significance or nonsignificance of several of the other variables under consideration.

Why do elderly patients turn down surgery while young men accept it? A number of possible answers to this question suggest themselves. It may be simply that older men are more fearful of the operation. They may believe that surgical mortality is greater among people of their age than among more youthful patients. Even though surgical deaths among the aged are declining, the patients' fears may remain. They possibly recall incidents in which elderly friends or relatives died on the operating table, and these recollections may intensify their own fears. In addition, older patients probably live more readily for the present or immediate future or yearn nostalgically for the past, whereas young patients are more prone to think further ahead and plan for life in the future. Faced with the necessity of maintaining good health and physical stamina in work and play, the young patient may rely more on surgery as a way of "cutting out my disease and living like a new man again." In contrast is the reluctance to surgical intervention of one "old timer," who stated, "I just have a couple of good years left. Why should I let them cut my body up?"

The young married patient has additional incentives for accepting surgery. Unlike the older, unmarried patient, he must assume the added roles of father and husband in addition to that of wage earner. He probably is less willing to return to family and work on a half cured–half disabled basis. Instead, he may feel obliged to avail himself of the possibilities of a complete cure, a cure which implies the eradication of the potentiality for spreading the disease to members of his family. A young father may gain the added courage necessary for accepting surgery through the realization that he must "act like a man," i.e., like a strong, courageous father. Visits and encouragement by wives before and during the operative period undoubtedly help considerably in reducing fears of surgery and feelings of lonely isolation (feelings which probably are quite intense among the older, unmarried patients).

Another factor which may help to explain the age difference in surgery refusal and acceptance is the amount of time, energy, and persistence exerted by the

ward physician or surgeon in persuading the patient to accept surgery. The medical staff generally advocates surgery more strenuously when it is recommended for the young patient. The doctor, on the other hand, is cognizant of the greater risk of medical complications attendant upon surgery with older patients. He also may sense a greater potential resistance among elderly patients who are "set in their ways" or who are less apt to go along with the recommendations of a younger resident or staff physician. As a consequence, the physician is less likely to try to "sell" surgery to a reluctant older patient.

The finding that patients with professional or managerial backgrounds are likely to accept surgery is not too surprising. As professionals or as individuals holding responsible positions, they probably are inclined to respect the professional recommendations of the hospital staff and to use mature judgment in weighing the long-term consequences of pulmonary surgery. The age factor may be a significant one in explaining the tendency for students to accept surgery. In addition, students, as well as professional and managerial people, may stress the importance of mental activities in daily living.[2] This may contrast with the high premium placed by the unskilled laborer on manual functions and the need to keep one's body intact. One patient, a former hard-working construction laborer, reflected such sentiments in his responses to the Madison Sentence Completion Form (4). He wrote, "When a patient is told he needs surgery . . . it's out of the question for me. The only time I'd take surgery is when I'm on a slab in a morgue. If they cut into my muscle I ain't worth two cents on the job."

The patient whose tuberculosis is service-connected in origin is apt to accept pulmonary surgery partly as a consequence of his being a younger man. (The mean age of the service-connected patients in this study was 33.4 years. The mean age of the nonservice-connected patients was 42.9 years). Over and above the age factor, however, the receipt of monetary benefits in the form of veterans compensation may serve as concrete evidence that the patient has a serious illness. On the other hand, the patient whose tuberculous disability is nonservice-connected may, in several instances, underestimate the extent of his disease and minimize the need for surgery. One such patient, for example, declared bluntly, "If I'm not sick enough to be eligible for compensation, I'm not sick enough to need an operation." Another patient adamantly refused to consider surgery while his claims for compensation were pending. His position on the matter was stated succinctly, "No money, no knife." As soon as he received his compensation he agreed to undergo surgery. He and several other patients expressed the opinion that they wished to have some means of subsistence to tide them over the difficult years ahead in case anything went wrong as a result of surgery.

If the observed data are condensed describing the "typical" patient who refuses surgery (older patient, unmarried, unskilled laborer, one whose tubercu-

[2] An attempt was made to investigate the relationship between educational background and surgery refusal. However, reliable data were not available for all of the subjects, and this phase of the study was abandoned.

losis was not contracted while in military service, and one who tends to leave the hospital without sanction), it may be seen that these data all relate to a certain type of personality structure and a way of life. To draw a generalized picture, this type of person has been unable to marry or stay married, is likely to be irresponsible, careless of self and others, more likely to be a drifter, is more likely to have poor frustration tolerance and poor long-range planning ability than those who accept surgery. Such a person would not have been able to learn a skill or a profession or to stick with any job (including that of "cure-taking"). Thus the demographic items which are associated with surgery refusal may not reveal factors *causing* refusal; but, rather, taken together with the fact of refusal, may delineate a type of poorly integrated personality.

The statistical findings suggest that the problem of surgery refusal has no general bearing on whether the patient is Negro or white. These results seem to run counter to certain suppositions that Negro patients are more apt to fear surgery or express a greater dread of physical mutilation, or show a greater resistance to undergoing major surgery performed by white surgeons. Several staff physicians, relying on clinical observations, suggested that young Negro patients would tend to refuse surgery and older Negro patients would tend to submit to surgery more readily than young and elderly white patients, respectively. A statistical analysis of the interaction of age and racial factors did not verify these hypotheses.

The absence of any significant relationship between medical factors and refusal of surgery was somewhat surprising. The present writers had anticipated that a greater proportion of patients with sputum positive for *M. tuberculosis* would accept surgery, in comparison with those having noninfectious sputum. It was assumed that "positive" patients would "give surgery a try" after reasoning that "if drugs won't convert me to negative, then surgery will." On the other hand, it was thought that many "negative" patients would turn down surgery under the rationalization that "I'm negative, so why should I risk surgery?" The above logic applied to predictions concerning the other medical variables as well.

Several suggestions may be offered to explain the nonsignificant statistical relationship between medical status and refusal of surgery. Perhaps the most cogent explanation is that the statistical research design used in this study may not have been sufficiently refined to "tease out" the importance of medical factors. Following this line of reasoning, it has been suggested that the refusal of surgery by certain types of patients may be a result of their far advanced disease in combination with additional influential factors. Conversely, the acceptance of surgery on the patient's part also may be a function of his extensive disease and other interreacting variables. For example, one group of patients may turn down surgery because they are in their sixties, or because they are persons whose extensive disease and their refusal of surgery both stem from a long-standing history of self neglect and poor judgment. Or they may refuse surgery because of the realization that they would still retain residual disease even after the operation. On the other hand, another type of patient may react to his extensive

tuberculosis and believe that "surgery is my only hope," and consequently would accept. Although the extent of disease may play a meaningful role among each of these individuals cited above, the influence of age, personality, and other significant variables may tend to obscure the over-all statistical results. A final explanation for these findings awaits a further study combining statistical and clinical methods of observation.

Summary

The purpose of this statistical study was to investigate several of the demographic factors which relate to the refusal of pulmonary surgery by patients with tuberculosis. One hundred and ninety-one tuberculous patients at this Veterans Administration hospital who refused surgery were compared with a hospital sample of 191 patients who accepted surgery, in terms of medical factors, age, race, marital status, occupational background, military service-connection, and type of hospital discharge. The subjects in this study were male military veterans. The generalizations obtained from the results of the study apply predominantly, therefore, to male patients in Veterans Administration hospitals.

The patients who were most likely to accept surgery were in the 20-year-old group, were more apt to be married than those who refused surgery, were more likely to be receiving a military service-connection disability compensation for tuberculosis, to have had a greater likelihood of previous employment in managerial or professional positions, or to have been students prior to hospital admission.

The patients who were likely to refuse surgery tended to be more than 50 years old, unmarried, not drawing compensation for service-connected tuberculosis, and were apt to be unskilled laborers. The patients who refused surgery were more inclined to be unsanctioned dischargees than those who accepted surgery.

The patient's medical condition alone, i.e., the extent of the tuberculosis (admission diagnosis), the unilateral or bilateral nature of the disease, the degree of infectiousness of the sputum, the number of sides recommended for surgery, the extent of recommended resection, and the original or re-treatment nature of chemotherapy, did not distinguish the patients who refused surgery from those who accepted it. The patient's racial background also had no clear-cut relationship to surgery refusal.

A future study is planned to investigate the individual psychological factors and patient-staff relationships which bear upon the tuberculous patient's decision to refuse pulmonary surgery.

Sumario

El Rechazamiento de la Cirugía entre los Tuberculosos

Tuvo por propósito este estudio estadístico investigar varios de los factores demográficos que se relacionan con la repulsa de la cirugía pulmonar por los enfermos de tuberculosis. Ciento noventa y un tuberculosos de un hospital de la Administración de Veteranos que rehusaron la cirugía fueron comparados con un grupo hospitalizado de 191 enfermos que aceptaron la cirugía, en términos de factores médicos, edad, raza, estado conyugal, situación profesional, relación con el servicio militar y forma del alta del hospital. Las generali-

zaciones derivadas de los resultados del estudio rezan, pues, predominantemente con los enfermos varones de los hospitales de la Administración de Veteranos.

Los pacientes más susceptibles de aceptar la cirugía quedaban en el grupo de veinte años de edad, tenían más probabilidades de estar casados que los que se negaban a operarse, tenían más probabilidades de recibir indemnización por incapacitación por tuberculosis en relación con su servicio militar y más probabilidades de haber ocupado antes puestos administrativos o profesionales o de haber sido estudiantes antes de su ingreso en el hospital.

Los enfermos más susceptibles de rechazar la cirugía solían tener más de cincuenta años, no estaban casados, no recibían indemnización por tuberculosis relacionada con su servicio militar y eran probablemente trabajadores inexpertos. Los que rehusaron la cirugía también se inclinaban más que los que la aceptaron a obtener altas inmerecidas.

Por sí solo, el estado médico, es decir, la extensión de la tuberculosis (diagnóstico al ingreso), la naturaleza uni- o bilateral de la dolencia, el grado de infecciosidad del esputo, la extensión de la resección recomendada y la índole, ya primaria o repetida, de la quimioterapia, no diferenciaba a los enfermos que rehusaron la cirugía de los que la aceptaban. Los orígenes étnicos del enfermo tampoco guardaron una relación bien definida con la repulsa de la cirugía.

Se proyecta otro estudio que investigue los distintos factores psicológicos y las relaciones de enfermo-personal que se enlazan con la decisión del tuberculoso que rehusa la cirugía pulmonar.

Resume

Le refus de l'acte chirurgical parmi les tuberculeux

L'objet de cette étude statistique était l'investigation de plusieurs facteurs démographiques en rapport avec le rejet de la chirurgie pulmonaire par le tuberculeux. Dans cet hôpital de la "Veterans Administration" 191 malades tuberculeux refusant de se soumettre aux opérations furent comparés avec un groupe de 191 malades de l'hôpital qui avaient accepté de se soumettre aux interventions chirurgicales. La comparaison était fondée sur les facteurs médicaux, l'âge, la race, l'état matrimonial, les conditions professionnelles, la situation militaire et les conditions du départ de l'hôpital. Les hommes étudiés étaient des anciens combattants. Les généralisations obtenues d'après les résultats de l'étude se rapportent donc à des malades tuberculeux de sexe masculin ayant été étudiés dans les hôpitaux de la "Veterans Administration."

Les malades acceptant l'opération appartenaient le plus souvent au groupe d'hommes de vingt ans, ils étaient ordinairement mariés, il y avait plus de chance qu'ils figurent parmi les pensionnés pour tuberculose contractée dans l'armée et qu'ils aient occupé antérieurement un poste de responsabilité, exercé une profession, ou fait des études avant l'admission à l'hôpital.

Les malades les plus aptes à refuser de se soumettre à l'acte chirurgical avaient le plus souvent plus de cinquante ans, ils n'étaient pas mariés, ne recevaient pas de pension pour tuberculose contractée dans l'armée et étaient ordinairement des travailleurs non spécialisés. Les malades n'acceptant pas les opérations étaient aussi les plus aptes à avoir quitté l'hôpital sans approbation médicale à l'encontre de ceux qui acceptaient les interventions.

Les conditions médicales seules, c'est-à-dire l'étendue de la tuberculose (diagnostic à l'admission) l'atteinte uni ou bilatérale, le degré d'infectiosité de l'expectoration, l'étendue de la résection préconisée ainsi que la nature de la chimiothérapie initiale ou renouvelée, ne permettaient pas d'établir une distinction entre les malades refusant d'être opéré et ceux qui acceptaient l'opération. Il n'existait pas de corrélation bien nette entre le refut de l'acte chirurgical et la race du malade.

Il est envisagé de procéder à une étude ultérieure destinée à l'investigation des facteurs psychologiques individuels et des rapports entre les malades et le personnel médical et infirmier de l'hôpital susceptible d'influencer le tuberculeux dans son refus d'accepter l'intervention chirurgicale.

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TUBERCULIN SKIN SENSITIVITY IN OLD AGE[1, 2]

O. D. BERESFORD

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Introduction

The incidence of pulmonary tuberculosis in old age has recently received much attention (1–3). The reason for such a substantial number of cases in old age seemed worth investigating, and it was decided to examine the tuberculin reaction in a number of old people. It is appreciated that the relationship between tuberculin skin sensitivity and resistance to tuberculosis is not clearly defined.

The investigation was confined to subjects more than sixty-five years of age. One group of people were in geriatric units and were suffering from a variety of chronic ailments, but the test was not performed on anyone who was acutely ill. The second group was composed of healthy subjects in old peoples' homes. No obvious difference was apparent in the results in the two groups and they are recorded together.

Methods

An intracutaneous (Mantoux) test was made on the forearm using 0.1 ml. of Old Tuberculin (Burroughs Wellcome) containing 10 TU. The test was read at seventy-two hours and, if there was no infiltration or if its diameter was less than 5 mm., a further intracutaneous test was made on the opposite forearm with 0.1 ml. of Old Tuberculin containing 100 TU. The test was read at seventy-two hours and, if there was no infiltration or if its diameter was less than 5 mm., the subjects were recorded as negative reactors to 100 TU.

Results

A total of 1,012 aged subjects were tested. In 19 cases, 12 females and 7 males, the second test was refused for various reasons. The results are recorded in table 1.

The high percentage of negative reactors was surprising. In the early phases of the study it was considered that this might be due to the physiologic condition of the skin. Particular attention was subsequently paid to this point, but there seemed to be no connection between the type of skin and the reaction. The eldest person tested was ninety-nine years old, and she reacted to 10 TU in spite of the lax, atrophied, and wrinkled skin associated with extreme old age. Fifty-four subjects more than ninety years old were tested in this investigation and 31 of them had positive cutaneous reactions to the tuberculoprotein. Eight of these subjects were positive to 10 TU.

The small number of positive reactors to 10 TU in this series makes it doubtful if a Mantoux test in such a dilution is worth doing in routine work with the older age groups. In table 2 may be seen the results of the reaction to 100 TU in successive age groups.

[1] From the Poole Chest Clinic, Dorset, England.

[2] This study was supported by a grant from the Research Committee of the South West Metropolitan Regional Hospital Board.

TABLE 1

TUBERCULIN SKIN SENSITIVITY IN THE AGED

Females			Males		
Number Tested	Per Cent Positive to 10 TU	Per Cent Positive to 100 TU	Number Tested	Per Cent Positive to 10 TU	Per Cent Positive to 100 TU
652	17.5	54.5	360	18.3	52.5

TABLE 2

RESULTS OF REACTION TO 100 TU IN SUCCESSIVE AGE GROUPS

Age Group	65–69	70–74	75–79	80–84	85–89	90 or More
Males (360)						
Number tested	43	75	95	94	39	14
Number positive to 100 TU	26 (60.2%)	47 (62.7%)	56 (59.0%)	50 (53.2%)	23 (59.0%)	9 (64.3%)
Females (652)						
Number tested	64	118	154	178	98	40
Number positive to 100 TU	37 (59.7%)	67 (56.8%)	84 (53.4%)	92 (51.6%)	56 (57.2%)	22 (55%)

It seemed improbable that so many people of this age group had never been infected with the tubercle bacillus. It was, therefore, decided to carry the investigation further in a group of 42 negative reactors to 100 TU. These subjects were tested simultaneously with four substances: 1,000 TU of OT, 1,000 TU of purified protein derivative (PPD), 5 TU of Depot Tuberculin, and a control substance containing the oily vehicle without tuberculin. One-tenth milliliter of OT, containing 1,000 TU, was injected intracutaneously into the right forearm, and on the same forearm 0.1 ml. of PPD (Weybridge) containing 1,000 TU was similarly injected. On the left forearm 0.05 ml. of Depot Tuberculin containing 5 TU of PPD was injected into the deeper layers of the skin, and on the same forearm 0.05 ml. of the control depot vehicle was also injected.

The results were read at seventy-two hours and at that time 17 subjects were negative to all substances. The OT and the PPD produced similar positive reactions in 21 subjects and the Depot Tuberculin was positive in 4 subjects who were negative to OT and PPD. However, the Depot Tuberculin was negative in 18 subjects who were positive to OT and PPD. No positive reactions were obtained for the control depot vehicle.

The site of the injection was watched carefully and after seven to ten days the Depot Tuberculin produced a positive reaction in all but 4 of the subjects who had been tested. These 4 were also negative to the OT and PPD.

It was considered that further evidence of pre-existing infection with tubercle bacilli could be obtained if those who had been tuberculin tested were also ex-

amined roentgenographically. The prime interest was in those who were negative reactors to OT but, as an incidental case-finding measure, it was decided to obtain roentgenograms on as many as possible of those who had been tuberculin tested. Immense difficulties were encountered in obtaining roentgenograms of these subjects. Many were bedridden, many refused to cooperate, and others were lost sight of. Altogether it proved possible to obtain films for 451 of the 1,012 patients tested. Large films were obtained on 192 persons and 259 were examined with miniature films. An additional 34 large films were taken in cases in which an abnormality was suspected on examination of the miniature film.

The presence of a calcified tuberculous lesion in the chest roentgenogram of an aged subject was often most difficult to determine with certainty, particularly if it was in the region of the hilum. Calcification of the costal cartilages and cross-sections of vessels or bronchi were particularly confusing. Calcified foci were only accepted if there was no reasonable doubt about the appearances, and it is probable that in the interpretation of these roentgenograms a number of calcified foci have been excluded because doubt existed. It was found that calcified foci could be detected quite satisfactorily in a miniature film, but in case of doubt a large film was also taken. Definite evidence of calcified foci was found in no fewer than 52 (29 per cent) of the negative reactors to 100 TU. Furthermore, in 7 subjects who were negative reactors, lesions were present which appeared to be tuberculous.

Discussion

Few surveys have been made of the tuberculin sensitivity of aged subjects. Jordon (4) records the results obtained in Minnesota for people more than sixty years of age, and these are substantially the same as in the present series. Amazon (5) and Groth-Petersen and Wilbek (6) noted an increase in the proportion of negative reactors in the older age groups. More recently Gianni and Sloan (7) have shown this trend, but the numbers tested were comparatively small. Their survey was carried out in Glasgow where the number of negative reactors was somewhat lower than in the present series. This may be accounted for by the greater incidence of tuberculosis in Glasgow and hence there is more opportunity for the aged to be in contact with the disease. Another factor which may account for the difference is that the present series is selected insofar as hospital in-patients and subjects in old peoples' homes were tested. It was not found possible to test a sufficient number of healthy old folk living in their own homes.

Our knowledge of the relationship between skin sensitivity and resistance is, at present, very incomplete; but, assuming there is some connection, then the presence of such a large number of negative reactors in this age group suggests a waning of resistance in old age. In this connection the work of Medlar (9) is of some interest. In a careful histopathologic study of 100 people who had died violent deaths he found evidence indicating that minimal pulmonary tuberculous lesions in older age groups represented a relatively new primary infection and in certain cases might represent second primary infections.

The age group of the present study is, in a way, a selected residue of their

generation as many will have succumbed to tuberculous infection in earlier age periods. The waning of resistance at this period of life is not peculiar to tuberculosis but occurs in other infections also. Why this should be so is not clear but many factors must play a part.

The evidence that previous infection with tuberculosis had occurred is shown by the large number in whom calcified foci could be demonstrated roentgenographically. These calcifications were presumed to represent the residuals of tuberculous lesions but further studies with the various fungal antigens were not made. Thompson (10) showed that calcified foci in English children indicated per se a past tuberculous infection and, owing to the rarity of histoplasmosis in Great Britain, this observation is generally believed to apply to older age groups. Amazon (5), in a roentgenographic survey of negative tuberculin reactors, showed evidence of previous tuberculous infection in 36 per cent. Groth-Petersen and Wilbek (6) found that 80 per cent of negative reactors previously had been infected as judged by pulmonary calcification. In the present series, 29 per cent of the negative reactors were shown to have been previously infected with tuberculosis.

Further evidence of previous infection with tuberculosis was demonstrated by the use of a Depot Tuberculin which produced a reaction in most of those who were negative to 100 TU. Presumably this occurred because the stimulus was more prolonged; but even so the reaction was delayed, compared with the time it took in younger age groups (8).

It is appreciated that certain workers do not agree that reactions to these larger doses of tuberculin have the same significance in terms of tuberculous infection as the skin reactions to small doses. Palmer and Petersen (11) presented evidence which suggested that skin reactions to large doses of tuberculin were nonspecific, probably as a result of tuberculin sensitivity produced by infection with other alcohol-acid-fast organisms.

A substantial number of cases of tuberculosis occur in old age and, as there is a high proportion of negative tuberculin reactors in this age group, it seems that the possibility of giving small doses of BCG to these people must be considered. The routine tuberculin testing of aged contacts will, therefore, be as important in the future as it has been with children and adolescents in the past. It also follows that more strenuous case-finding measures must be extended to this age group.

Summary

The tuberculin skin sensitivity of 1,012 people more than sixty-five years old was tested and the results showed a high proportion of negative reactors to 100 TU of Old Tuberculin.

Chest roentgenograms of these negative reactors showed that in 29 per cent there was roentgenographic evidence of previous infection with tuberculosis. Further evidence of previous infection with tuberculosis was provided by the use of a Depot Tuberculin which produced a reaction in most of the nonreactors to 100 TU.

The suggestion is made that routine tuberculin testing of the aged should be carried out in contact examination, and the advisability of giving small doses of BCG should be borne in mind.

Sumario

La Cutisensibilidad a la Tuberculina en la Ancianidad

Se determinó la cutisensibilidad a la tuberculina de 1,012 personas de más de sesenta y cinco años, revelando los resultados una elevada proporción de sujetos negativos a 100 U.T. de tuberculina antigua.

Las radiografías torácicas de esos sujetos negativos revelaron en 29 por ciento signos radiográficos de infección anterior por tuberculosis. Aportó nueva prueba de esta infección anterior el uso de otra tuberculina que produjo una reacción en la mayor parte de los que no habían reaccionado a 100 U.T.

Se ofrece la indicación de que se lleve a cabo la comprobación sistemática con tuberculina de los ancianos en examen por contacto y que se tenga presente la conveniencia de administrar pequeñas dosis de BCG.

Resume

Sensibilité de la peau à la tuberculine dans la vieillesse

La sensibilité à la tuberculine de 1012 sujets âgés de plus de soixante-cinq ans a été testée et les résultats ont révélé une grande proportion de réactions négatives à 100 unités de tuberculine de Koch (OT).

Les radiogrammes du poumon des sujets à réactions négatives révélaient chez 29% d'entre eux les signes d'une infection tuberculeuse antérieure. D'autres preuves d'infection tuberculeuse antérieure étaient obtenues avec l'inoculation de tuberculine "retard", qui déterminait une réaction dans la plupart des cas à réaction négative à 100 UT.

L'auteur suggère de procéder systématiquement aux tests à la tuberculine chez les vieillards à l'occasion des examens de dépistage des "contacts" et de se souvenir qu'il y a intérêt à administrer de petites doses de BCG.

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Case Reports

A POSSIBLE CASE OF PULMONARY MONILIASIS[1]

PAUL W. SCOTT

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Introduction

Pulmonary moniliasis, an infection of the lungs with *Candida albicans*, was first described half a century ago. In spite of numerous case reports and a great deal of experimental work in the intervening years, the incidence and even the existence of this disease are still in dispute. Many of the reported cases have been questionable, and probably the disease is often diagnosed without sufficient evidence. The purpose of this paper is to define the criteria by which the diagnosis can be made and to present a possible case of the disease.

Castellani described a case of "tea tasters' cough" in Ceylon in 1905 (1). This was caused by snuffing up dried tea leaves heavily contaminated with Monilia. The first case reported in the United States was in 1915 by Boggs and Pincoffs in Baltimore (2). Since that time there have been numerous case reports of pulmonary moniliasis, both primary infections with Candida and infections secondary to another chronic disease. In one series of 15,845 consecutive autopsies, each of the 25 cases of candidiasis was a complication of a debilitating or fatal disease (3). In recent years moniliasis following antimicrobial therapy has been widely recognized. Although a few antimicrobials directly enhance the growth of *Candida albicans*, this is not the mechanism by which antimicrobial treatment causes moniliasis. Those antimicrobials which do not stimulate the growth of Candida are equally capable of producing moniliasis. The mechanism is generally thought to be that suppression of the normal flora allows the yeast to become predominant.

Observations

Clinical Findings

Pulmonary moniliasis is usually a slowly progressing febrile disease with night sweats, dyspnea, pleural pain, fatigue, and weight loss. The most troublesome symptom is a persistent productive cough. The sputum is characteristic. It is mucoid, tenacious, and gelatinous, with the odor of bread or yeast. It has been described as "glairy," "curdy," "lumpy," "stringy," "gruel-like," or "like cooked tapioca." Occasionally it contains blood or small gray flakes made up of fungi and cellular debris. The physical signs are not very helpful in distinguishing this disease from other chronic pulmonary diseases. There may be sticky rales, signs of consolidation, and, less often, signs of cavitation or pleural effusion. In general, the patient does not appear to be as sick as one would anticipate from the roentgenographic findings. If the disease is severe, it may mimic advanced pulmonary tuberculosis.

Roentgenographic Findings

Roentgenographic findings are quite variable. Seabury emphasizes the fact that no reliable roentgenographic criteria exist to differentiate pulmonary mycoses from each

[1] From the Department of Internal Medicine, State University of Iowa Hospitals, Iowa City, Iowa.

other or from tuberculosis (4). In early stages, the lesions often are diffuse, with infiltration extending outward from the hila. Occasionally there is patchy infiltration resembling bronchopneumonia except that the lesions are less sharply outlined (5). This gives a fluffy, cotton-like appearance. Sometimes there is cavitation. Usually both lungs are affected, the apices being spared at first. Extension or regression of lesions is seen on serial films. Long-standing moniliasis is said to result in chronic interstitial fibrosis extending outward from the hila with beading along the fibrotic lines (6).

Diagnosis

The diagnosis of pulmonary moniliasis, especially the primary type, is extremely difficult. Numerous factors are responsible for this. The greatest trouble is that *Candida albicans* exists as a saprophyte in the sputum of normal persons. The incidence varies considerably but averages 30 to 40 per cent of the population. Although it is frequently found in the sputum of normal persons, it does not normally occur within the bronchial tree. Therefore, its presence in bronchial washings suggests infection, but is not diagnostic.

Skin tests are of no value. Serologic tests are more helpful, but many apparently uninfected people have agglutinins to *Candida albicans*, 31.6 per cent in one series of 2,000 patients. The percentage of positive tests in normal persons varies considerably in different reports. Agglutination tests have been used most often, but Peck and associates got more satisfactory results with a complement-fixation test (7). In a series of unselected patients with dermatoses, only 13.5 per cent had positive reactions, whereas 75 per cent of those with monilial skin infections had positive tests. There was no correlation between positive complement-fixation tests and positive stool cultures for *Candida albicans*.

The only method of establishing conclusively the diagnosis of pulmonary moniliasis is the demonstration by lung biopsy of the presence of Candida within the lung tissue and the absence of other etiologic agents. When biopsy is not performed, however, one should be suspicious of moniliasis if there is clinical and roentgenographic evidence of pulmonary infection; if *Candida albicans* is grown consistently in large numbers from uncontaminated sputum, including that obtained by bronchoscopy, and if the presence of tuberculosis, bronchiectasis, cancer, pyogenic infection, and other mycoses is excluded by appropriate studies. Prompt response to appropriate treatment for moniliasis alone without other antimicrobial drugs gives additional support to the diagnosis.

Treatment

There is no standard treatment for pulmonary moniliasis. Bed rest is usually advised. The drug most frequently prescribed is potassium iodide in large doses, up to 6 gm. a day. Favorable response to anti-*Candida albicans* rabbit serum has been reported (8). However, immunization of rabbits with dead yeasts or sublethal doses of living organisms produces agglutinins to *Candida albicans* but does not give any protection to subsequent injection of a lethal dose of organisms (9). There have been some recent favorable reports of using brilliant green dye by aerosol (10, 11), Pentamidine® (12), and hydroxystilbamidine (13). A few case reports of "systemic moniliasis" successfully treated by nystatin have been published (14), but the evidence is unconvincing and there is little to suggest that oral nystatin is effective outside the gastrointestinal tract (15). The ordinary antimicrobials, corticotropin, and cortisone are contraindicated. Amphotericin B, one of the newer fungicides, has been successful in several cases. For the time being, potassium iodide is probably the drug of choice.

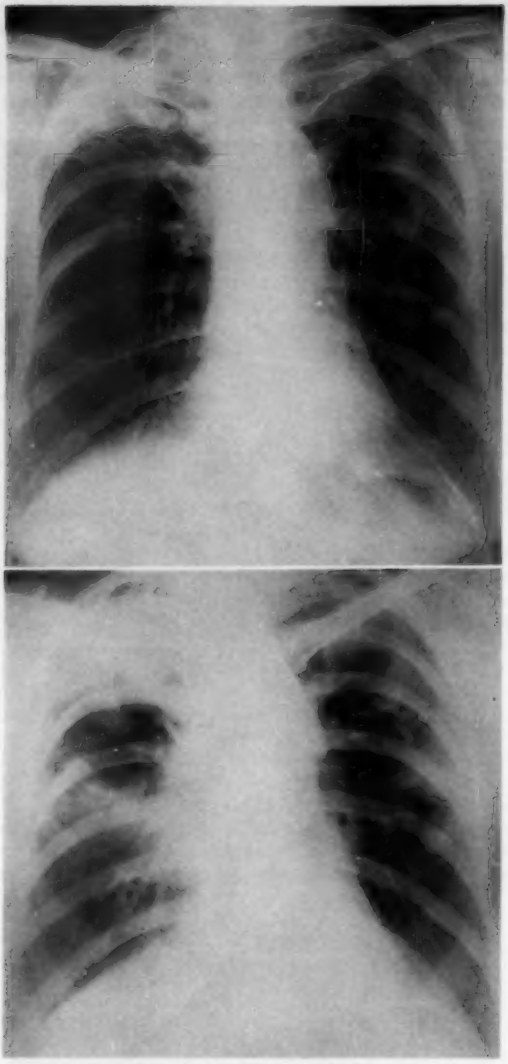

FIG. 1 (Upper). Roentgenogram of August 30, 1954, showing dense linear infiltration of the right apex and moderate infiltration of the peripheral portion of the left upper lung field

FIG. 2 (Lower). Roentgenogram of September 7, 1954. The disease had spread in both lungs, and the right middle lobe was densely infiltrated.

Case Report

On September 28, 1954, a 52-year-old white widow came to the State University of Iowa Hospitals. She had been well until two or three months previously, when she developed night sweats, cough, and a low-grade fever. The night sweats had been profuse at the onset

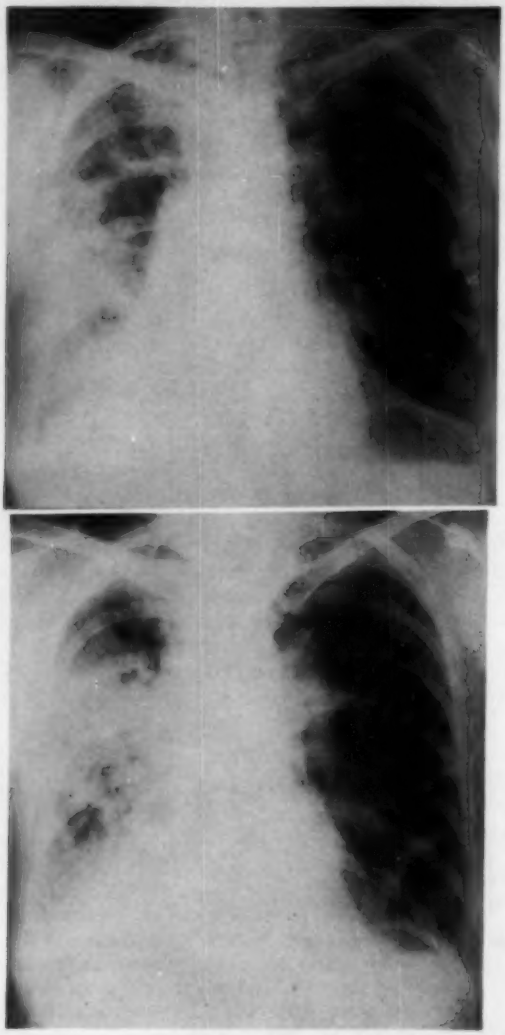

Fig. 3 (Upper). Roentgenogram of October 1, 1954, showing a cavity with fluid level in the right midlung field posteriorly.

Fig. 4 (Lower). Roentgenogram of October 26, 1954. The lower right lung was cleared slightly, but a new area of infiltration appeared in the left upper lung field.

but had decreased in intensity. The cough was almost entirely nocturnal. It was productive of a small amount of mucoid sputum, with no blood or pus at any time. With the cough, there was often mild wheezing. The patient's temperature was about 101° F. each evening. There had been a 15 pound weight loss, slight fatigability, but no chills, dyspnea, chest pain, or gastrointestinal or genitourinary symptoms. The patient believed that her symptoms were due to "nerves." She had received no antimicrobials before her symptoms appeared, but in August and early September, tetracycline, penicillin, streptomycin, and isoniazid had been given without effect.

Past history: For three or four years, the patient had had frequent nasal stuffiness, wheezing, and cough sometimes productive of mucoid sputum. These symptoms were worse during the summer and had been considerably relieved by desensitization to ragweed and mold in 1951. Several members of her family had had bronchial asthma or bronchitis.

Physical examination: On physical examination the blood pressure was 132 systolic, 70 diastolic in mm. of mercury, the pulse 96 per minute, and respirations 20. She did not appear to be ill. There was no lymphadenopathy, and no monilial infection of the nails was noted. There was an increase in the bronchial quality of the breath sounds at the right apex, but the chest was otherwise normal. There were no rales. The heart was normal. The spleen and liver were not palpable.

Skin tests were as follows: negative to 1:100 Old Tuberculin; negative to second-strength PPD; positive to histoplasmin, 1:100. Sigmoidoscopy was normal. Bronchoscopy was performed at a private hospital and was repeated at the University Hospitals. The first examination was normal except for some sticky secretions in the orifice of the left upper lobe. Five weeks later there was only a slight narrowing of the right lower lobe bronchus, which contained minimal mucoid secretion.

Laboratory findings: A urinalysis was normal. The hemoglobin ranged from 9.5 to 11.8 gm. per 100 ml. The leukocyte count averaged 18,000 per cu. mm. but ranged from 11,000 to 26,000 with 74 per cent neutrophils and 8 to 10 per cent eosinophils. The sedimentation rate (Westergren) was 103 mm. per hour. Blood urea nitrogen was normal. The plasma proteins were 7.7 gm. per 100 ml. with 3.9 albumin and 3.8 globulin. Liver function tests were normal except for a thymol turbidity of 11.5 units. Serologic tests for syphilis were negative. Cold agglutinins were not present. Complement-fixation tests were negative for *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. Agglutination tests were negative for *Cryptococcus neoformans*, *Sporotrichum schenckii*, and were positive for *Candida albicans* at a dilution of 1:1,280. Gastric washings were consistently negative for tubercle bacilli by smear, culture, and guinea pig inoculation. Culture of gastric washings yielded *Pseudomonas aeruginosa* and *Aerobacter aerogenes*. Papanicolaou stains of the sputum were negative for malignant cells. Bronchoscopic aspirations, sputum, gastric washings, and stools consistently produced a heavy growth of *Candida albicans* on culture. Several stools contained occult blood but no ova or parasites. Bone marrow culture was sterile. Roentgenograms of the paranasal sinuses, upper gastrointestinal tract, and colon were normal.

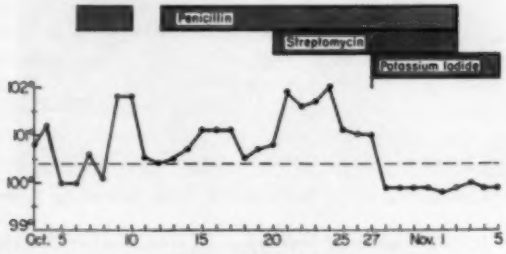

FIG. 5. Temperature chart showing maximal daily rectal temperatures. Temperatures in August and September were similar to the pre-iodide portion of this graph.

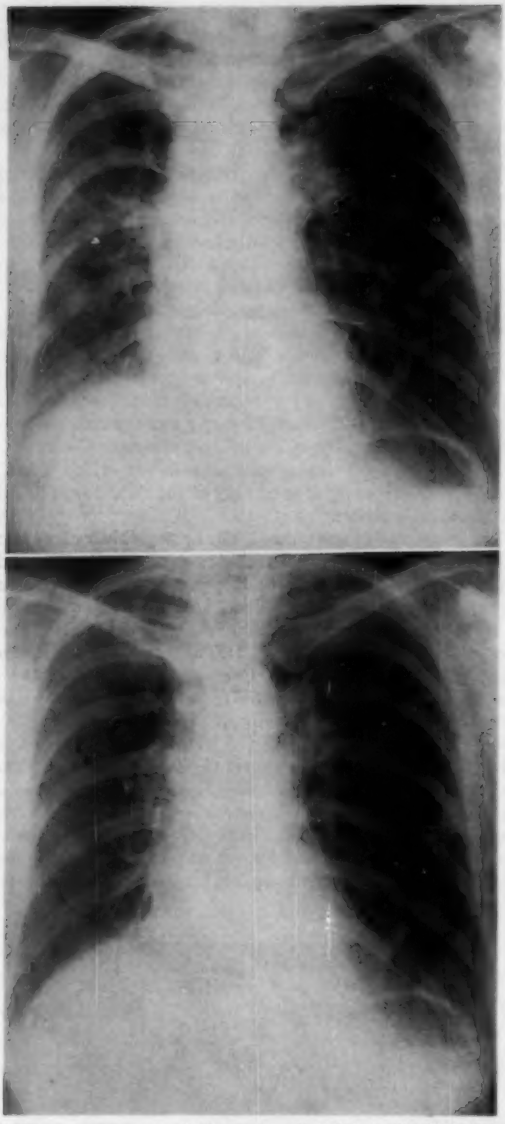

FIG. 6 (Upper). Roentgenogram of November 2, 1954, indicating improvement in appearance of chest.

FIG. 7 (Lower). Roentgenogram of November 16, 1954; further clearing had occurred, with only minimal residual fibrosis.

Chest roentgenograms: On August 30 a chest film showed a dense linear infiltration of the right apex and moderate infiltration of the peripheral portion of the left upper lung field (figure 1). One week later the lesion had spread considerably in both lungs, and the right middle lobe was densely infiltrated (figure 2). Three weeks later, when the patient was first seen at the University Hospitals, the left lung had cleared, the right apex had partially cleared, and the right middle and lower lobes were massively involved. There was a cavity with fluid level in the right midlung field posteriorly (figure 3). These roentgenographic densities were soft, patchy, fluffy in outline, extending and regressing from week to week.

Course in the hospital: In the hospital the patient continued to have only minimal symptoms with a daily rectal temperature of about 101° F. The pulse averaged 90 to 100 per minute. Her cough and night sweats lessened, but the fever and chest films did not improve. She did not appear to be as ill as one would expect from her chest films. After a week the patient was started on penicillin with no apparent effect; two weeks later streptomycin was added without benefit. A white plaque, which was shown to be pure Monilia by smear and culture, appeared on the tongue. For the first two weeks chest films showed only minor changes in the pulmonary infiltrate. Four weeks after admission the right lower lung field was clearing somewhat, but a new area of infiltration had appeared in the left upper lung field (figure 4). At this time, the tentative diagnosis of pulmonary moniliasis was made because of the development of thrush on the tongue; repeated culture of Monilia from bronchoscopic aspirations, sputum, gastric washings, and stools; failure to demonstrate any other etiologic agent; failure to respond to antimicrobials; positive agglutination for *Candida albicans* at a high titer; and suggestive roentgenographic findings.

Treatment with 0.6 gm. of potassium iodide every eight hours was started. There was no preliminary desensitization. The next day for the first time in months the patient's temperature was normal, and thereafter she had no fever (figure 5). Within a week she was completely asymptomatic and her chest film was considerably improved (figure 6). Further clearing occurred with only minimal residual fibrosis (figure 7). Six days after starting iodide treatment, penicillin and streptomycin were discontinued. The lesion on the patient's tongue cleared after bicarbonate of soda mouth washes and gentian violet. After discharge she continued to take 0.6 gm. of potassium iodide three times a day for more than six months. She remained asymptomatic except for nasal stuffiness and postnasal drip.

Three years later the patient was still well and her chest film was unchanged. Her vital capacity was 90 per cent of normal and there was a sixteen-fold decrease in her agglutination titer for *Candida albicans*.

Discussion

The history and physical findings were of little help in determining the type of chronic lung disease present. Mycotic infection was suggested by the patient's appearance of well-being when her chest films showed progressive, far advanced pulmonary disease. Her history of allergy suggested Löffler's syndrome. Several authors have mentioned the susceptibility of allergic persons to pulmonary moniliasis (16). Some have suggested that the allergic symptoms are results of chronic moniliasis rather than precursors (17, 18). The development of thrush resulted from the tongue's almost constant contact with heavily contaminated sputum. The leukocytosis is consistent with other experience. The anemia may have resulted from gastrointestinal infection, with blood loss. Tests for occult blood in the stool became negative on iodide therapy. The high level of globulins and the elevated thymol turbidity may have been caused by liver involvement. The apical infiltration of the first chest film does not conform with the accepted location of the earliest lesions. It is not possible, however, to determine the first area infected by such a rapidly moving lesion.

Summary

Pulmonary moniliasis is an active, progressive infection of the lungs with *Candida albicans*. It cannot be distinguished from other chronic pulmonary infections by history or

physical examination. Certain features suggest this disease, but it can be diagnosed with certainty only by lung biopsy. The presence of tuberculosis, tumor, other mycoses, bacterial infections, or bronchiectasis must be excluded before the diagnosis of primary pulmonary moniliasis can be made.

A possible case of pulmonary moniliasis which showed dramatic response to potassium iodide has been presented.

Sumario

Posible Caso de Moniliasis Pulmonar

La moniliasis pulmonar es una infección progresiva y activa de los pulmones por *Candida albicans*, que no puede diferenciarse de otras infecciones pulmonares crónicas por la historia o el examen físico. Ciertas características apuntan a la enfermedad, pero no cabe diagnosticarla con seguridad más que con la biopsia pulmonar. Antes de poder hacer el diagnóstico de moniliasis pulmonar primaria, hay que excluir tuberculosis, tumor, otras micosis, infecciones bacterianas y bronquiectasia.

Se presenta un posible caso de moniliasis pulmonar que reveló una respuesta teatral al yoduro de potasio.

Resume

Moniliase pulmonaire probable

La moniliase pulmonaire est une infection évolutive due à la localisation de *Candida albicans* dans le poumon. L'examen physique ni les antécédents ne permettent de la distinguer d'autres infections pulmonaires chroniques. Certains aspects suggèrent le diagnostic de moniliase pulmonaire, mais il n'y a que la biopsie pulmonaire qui puisse le confirmer. Il y a lieu d'éliminer d'abord les diagnostics de tuberculose, tumeurs, infections bactériennes, bronchectasie ou d'autres mycoses avant de conclure à celui de moniliase pulmonaire primaire.

Présentation d'un cas de moniliase pulmonaire probable ayant réagi favorablement à l'administration d'iodure de potassium.

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SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS DURING CORTICOSTEROID THERAPY OF DISSEMINATED LUPUS ERYTHEMATOSUS[1]

MARVIN S. HARRIS, MAURICE HYMAN, AND ALAN J. FRIEDMAN

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INTRODUCTION

The use of the corticosteroids in the management of infectious diseases has varied with the accumulation of clinical experience and the results of animal experimentation.

Because of an almost immediate sense of well-being and what seemed to be clinical improvement associated with the use of corticosteroids in various infections, these drugs were widely used for a while on an empiric basis. It was not long before reports appeared showing that a therapeutic paradox existed, i.e., the patient might temporarily feel much better but the actual infection was either not improved or actually was made worse (1–4).

Accentuation of infectious diseases was shown conclusively in animal experimentation. Infections to which the animals were subjected were made more virulent. In some instances, enhancement of susceptibility could be induced (5–7). As early as 1950 it was demonstrated that experimental tuberculosis could be increased in virulence with steroids (8)

The danger of activation of tuberculosis by the use of steroids was the subject of an editorial (1) in 1951. The theoretic danger was pointed out and case reports were cited. Subsequent to this plea for caution, numerous cases were documented demonstrating the tendency of steroid therapy to cause tuberculous lesions to appear and progress in what had previously been apparently normal lungs.

Once the danger of indiscriminate use of the corticosteroids was appreciated, the next therapeutic phase consisted of attempts to gain the benefits of the steroids and to minimize the dangers with the simultaneous use of antimicrobial drugs in patients with clinical tuberculosis. Meyer and associates (7) used combined antimicrobial therapy and corticosteroids in 1952 in an attempt to prepare the tracheobronchial tree for surgery. They noted a dramatic improvement in the bronchoscopic appearance of the lesions. However, neither of the two patients selected for surgery survived; one died of a bronchopleural fistula, and the other of left ventricular failure. In 1953 the possibility of combined therapy in tuberculous meningitis was successfully explored by Shane and Riley (9). This concept was pursued further by the use of combined therapy in cases of disseminated lupus erythematosus associated with active pulmonary tuberculosis (10).

It may be, therefore, that combined therapy with antimicrobial drugs and corticosteroids will prove feasible not only in tuberculosis, but also in instances in which the corticosteroids are necessary for nontuberculous disease. In this report a case is presented wherein tuberculosis developed during the course of corticosteroid therapy for lupus erythematosus. The tuberculosis was controlled and a successful lobectomy for cavitary tuberculosis was performed under a multiple drug regimen.

CASE REPORT

L. P., a 33-year-old female, was admitted to the Cedars of Lebanon Hospital on July 6, 1956, with chief complaints of fever and hoarseness for one month and repeated, copious hemoptyses for three days.

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[1] From the Medical Service and Thoracic Surgical Service of Cedars of Lebanon Hospital, Los Angeles, California.

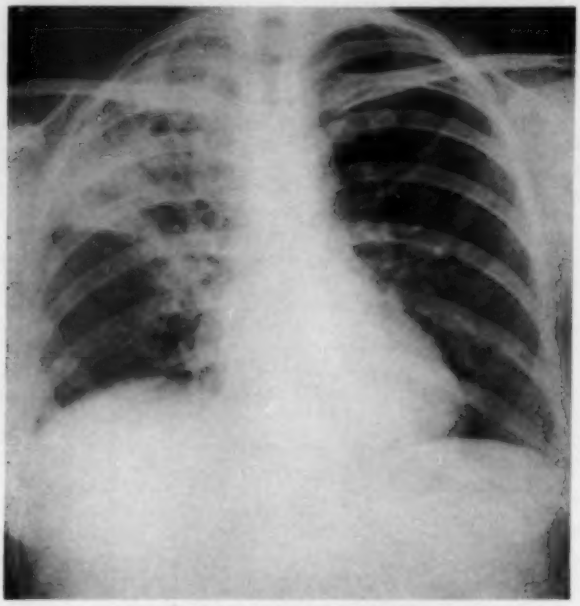

FIG. 1. Chest roentgenogram obtained upon admission to the hospital showing diffuse minimal changes in the left lung and extensive disease of the right lung.

She had suffered with migratory joint pains and swellings since 1948, for which she had continued to receive considerable treatment, varying from acetylsalicylic acid to injections of gold and sodium thiosulfate. The only effect was various allergic reactions but no benefit to the joint involvement. Later the patient began to experience bouts of fever associated with increasingly severe joint involvement, and in 1950 and 1951 received two-week periods of treatment with corticotropin. This relieved her complaints partially, and she was able to be moderately active. In 1953 she experienced a complete remission of her complaints during pregnancy, which she carried to term, and she delivered a normal female child. Her joint symptoms flared up again two weeks post partum, more severely than ever, and for the next year these symptoms were partially controlled by 10 units of corticotropin daily.

In November, 1954, a small infiltrate appeared in the right midlung field. Thorough investigation of this infiltrate failed to provide a diagnosis, and the lesion is said to have disappeared under observation. During 1954 and the succeeding period, the patient began to experience recurrent bouts of "pleurisy" associated with fever, but not always with joint pains. These manifestations were controlled by salicylates and, on occasion, corticotropin and sulfonamides, and they sometimes subsided without treatment. A particularly severe bout of such illness developed in June, 1955, and at this time a diagnosis of systemic lupus erythematosus was made on the basis of several demonstrations of lupus erythematosus cells in the peripheral blood. She was then given prednisone in doses of 10 to 30 mg. daily, depending on the severity of complaints. Usually she took 10 or 15 mg. daily, but about every three months fever, which rose to 103°F., as well as joint and chest pains required 30 mg. daily for control. In May, 1956, the patient began to have fever more frequently, as well as cough and hoarseness. Because of these symptoms, which were thought by her physician to be related to the lupus, the prednisone dosage was increased to 30 mg. On July 3 an hemoptysis occurred, and this recurred several times daily until she was admitted to the Cedars of Lebanon Hospital on July 6, 1956.

FIG. 2 FIG. 3 FIG. 4

FIG. 2. Roentgenogram obtained on August 17, 1956, demonstrating a contractive process in the right upper lobe and a concavity of the lower border.

FIG. 3. Roentgenogram obtained on November 13, 1956, indicating further clearing and contraction on the right side; the right lower lobe shows considerable clearing and is almost normal.

FIG. 4. Postoperative appearance of chest.

Physical examination disclosed a fairly well-nourished white female, moderately dyspneic, apprehensive, with fresh blood in the mouth, the result of recent hemoptyses. The pertinent physical findings were limited to the chest, where a right-sided lag was noted and dullness was elicited over the upper lobe. Breath sounds were bronchial in character with a quality varying from tubular to amphoric over the right upper lobe. Bronchovesicular breathing was noted over the right middle and lower lobes. Many medium and fine rales accompanied both phases of the respiratory murmurs. A roentgenogram of the chest disclosed far advanced pulmonary tuberculosis, involving the right upper lobe in a partly atelectatic and caseopneumonic process, in which several punched-out cavities appeared. A diffuse nodular dissemination was present in the right middle and lower lobes. The left lung showed diffuse minimal changes (figure 1). The sputum on direct smear contained many acid-fast bacilli which in subsequent culture showed characteristics typical of *M. tuberculosis*. Study of the peripheral blood was positive for lupus erythematosus cells.

The patient was started on streptomycin, 1 gm. three times weekly; PAS, 12 gm. daily; and isoniazid, 300 mg. daily. On July 10 the patient was transferred to Maryknoll Sanatorium in Monrovia. During the next four months she exhibited progressive improvement in her chest condition, best reflected by the following roentgenographic reports:

August 17, 1956 (figure 2). There is a contractive process involving the right upper lobe resulting in an upward displacement of the fissure and a concavity of the lower border of the upper lobe. Within the upper lobe, which is largely occupied by diffuse nodular disease, there is at least one area of rarefaction suggestive of a cavity. Throughout the remainder of the right lung are many nodular lesions, partly discrete and partly confluent, but with no evidence of breakdown. The right diaphragm is elevated. The left lung is essentially clear.

October 1, 1956. Films show progressive clearing on the right side with contraction of the right upper lobe; the right lower lobe shows clearing.

November 13, 1956 (figure 3). There is further clearing and contraction on the right side, although there is apparently an area of cavitation just behind the mesial end of the right clavicle. The right lower lobe has shown considerable clearing and is almost negative at this time.

During this period, there was one episode that might have been a flare-up of the lupus symptoms and this was controlled by an increase in the dose of prednisone to 20 mg. daily from the minimal maintenance of 7.5 mg. which ordinarily controlled her symptoms.

Despite the clinical improvement which paralleled the roentgenographic changes noted above, the sputum remained positive for acid-fast bacilli on microscopy, and in November the following conclusions were reached: (*1*) that the patient had received close to the maximal expected benefit from chemotherapy and bed rest and that definitive treatment in the form of surgical resection would be necessary; (*2*) that such resection should be carried out while the lupus was in remission; (*3*) that the resection should be done while there was reasonable expectation that the patient's tubercle bacilli were still susceptible to the antituberculous drugs.

Accordingly, the patient was transferred to the Cedars of Lebanon Hospital on November 25. Planigrams confirmed the presence of the cavity in the apex of the right upper lobe. Bronchoscopy on November 27, which included thorough inspection of all orifices through the right-angle viewer, disclosed that all of the visible mucopurulent material was coming from the upper lobe and that no ulceration or stenosis was present. It was also considered a significant step in evaluation that the patient tolerated the stress of the procedure, as well as the topical and thiopental sodium anesthesis without disturbance.

On December 1, 1956, a right upper lobectomy was performed by Dr. Hyman. The operative procedure was as follows: The right chest was entered through a standard posterolateral thoracotomy incision in the fifth interspace. There was a complete pleural sym-

FIG. 5. Resected right upper lobe with cavity.

physis. The upper lobe was considerably shrunken and appeared to contain a mass. The middle and lower lobes appeared to be free of disease and expanded sufficiently to almost fill the hemithorax. The arteries and veins to the upper lobe were isolated, ligated, and severed. The bronchus was amputated flush with the main stem bronchus and was closed with interrupted 000 silk. Pleuralization of the bronchial stump was carried out. The phrenic nerve was crushed. The chest was closed in a routine manner after the insertion of two catheters. The patient received 1,000 ml. of blood during the procedure and left the operating room in good condition. The resected lobe was described as follows:

Gross description (figure 5): A 75 gm. right upper lobe measured 9 by 6 by 3.5 cm. The pleural surface was covered by small dense adhesions. Dissection of the apical segmental bronchi led to a cavity measuring 3.5 by 2.3 by 0.5 cm. The cavity was empty; the walls were well formed and surrounded by a thin hyaline zone. The remainder of the pulmonary parenchyma showed scattered spots of light caseous material, 0.3 cm. in diameter.

Microscopic description: The specimen showed caseonecrotic and miliary tubercles with

fibrosis and alveolar metaplasis. The wall of the cavity was lined by granuloma. Special stains showed acid-fast rods (figure 5).

On the day prior to surgery the patient had been given 100 mg. of hydrocortisone intramuscularly and this dose was given twice on the day of surgery: 100 mg. before surgery and 100 mg. on completion of the operative procedure. A similar dose was given the following day, and thereafter doses of 50 mg. were given only when the pulse became more rapid or the blood pressure fell below 110 systolic in mm. of mercury. Two such doses were necessary but by the fifth day the patient was taking only prednisone in doses of 10 mg. daily.

The postoperative course was unusually smooth; the patient was alert and responsive only a few hours after being returned to her room, and was able to take liquid nourishment that evening. She was moving about freely in bed on the second day. Sputum specimens collected on December 3 and December 8, the latter a three-day specimen, were both negative for *M. tuberculosis* on concentrate and subsequently proved to be negative for *M. tuberculosis* on culture. At this writing eight more concentrates and cultures of three-day sputum collections have been "negative."

Roentgenograms of the chest (figure 4) now show only the reduction of the right lung as the result of the lobectomy. The patient is free of all local and constitutional symptoms, and within the fourth postoperative month ambulation was begun and the patient was allowed to return to her home five months after surgery. The symptoms of lupus have not recurred despite the reduction of her daily prednisone dosage to 5 mg. No attempt has been made to stop the drug entirely. Triple antituberculous drug therapy as well as partial bed rest are being continued.

Discussion

The finding of lupus erythematosus cells in the peripheral blood or marrow is regarded by some as diagnostic of systemic lupus, particularly in the presence of a compatible clinical picture (11). On the other hand, some clinicians have noted the presence of these cells in what otherwise qualifies for rheumatoid arthritis (12). Furthermore, these cells have been reported in the course of corticoid therapy, especially during periods when added stress or corticoid withdrawal produced a state of relative corticoid insufficiency (13–14). Under these circumstances the diagnosis of lupus in the present case may be open to question. In the final analysis, no organ or systemic involvement other than involvement of the joints can be ascribed to lupus; the bouts of fever, pleuritic pain, and general malaise may well have been a phase of tuberculous dissemination. Favoring lupus, however, are the facts that lupus erythematosus cells were found at least twice before any sustained corticoid therapy had been given, that the course of the disease was prolonged, and that residual joint deformity is completely absent now that the disease is quiescent.

Regardless of the diagnosis of lupus erythematosus, the essential point to be affirmed by the present report is that, when necessary, corticoid therapy need not interfere with the adequate treatment of pulmonary tuberculosis. In fact, some clinicians are now beginning to believe that it may aid such treatment, preventing premature walling off of active areas by fibroblastic activity (15) and by preventing blocks in the cerebrospinal canal in the case of tuberculous meningitis (16). This now seems to be the logical and reasonable role of the corticoids, first having gone through the tragically disappointing period when because of their anti-inflammatory effect these drugs seemed to offer definitive treatment for tuberculosis. This short-lived phase gave way to the period in which the danger of spreading the infection under the camouflage of these agents prevented their judicious application in situations in which their action might have been valuable. The third phase is now present, and it is the purpose of this report to add this small bit of evidence that corticoid therapy need not interfere with the adequate management of pulmonary tuber-

culosis and that adequate management may even include surgical resection during effective chemotherapeutic control. Such control apparently is the key to the safe use of the corticosteroids (17).

Summary

The history of a patient with systemic lupus and intervening pulmonary tuberculosis is described. Definitive medical and surgical treatment of both conditions was carried out without mutual interference. Treatment of the lupus consisted of small maintenance doses of prednisone, increased at times when a recrudescence of symptoms demanded. Treatment of the tuberculosis consisted of isoniazid-streptomycin-PAS and bed rest, climaxed by resection of a destroyed right upper lobe at what was judged to be the optimal time.

The lupus is now in remission and the tuberculosis is successfully resected, with 8 cultures of the sputum negative for *M. tuberculosis* in the six months following surgery.

Sumario

Tratamiento Quirúgico de la Tuberculosis Pulmonar durante la Corticoesteroidoterapia del Lupos Eritematoso Diseminado

Descríbese la historia de un enfermo que tenía lupus generalizado y tuberculosis pulmonar asociada. Sin mutuo impedimento, se llevó a cabo el tratamiento médico y quirúrgico definitivo de ambas dolencias. El tratamiento del lupus consistió en pequeñas dosis de sostén de prednisona, aumentadas a veces cuando así lo exigía la recrudescencia de los síntomas. El tratamiento de la tuberculosis pulmonar comprendió isoniacida-estreptomicina-PAS y descanso en cama, coronado esto por la resección de un lóbulo superior derecho destruído en el momento que pareció óptimo para ello.

El lupus se halla ahora en remisión y la resección logró éxito en la tuberculosis, con ocho cultivos del esputo negativos para el *M. tuberculosis* en los seis meses consecutivos a la operación.

Resume

Traitement chirurgical de la tuberculose pulmonaire au cours de la corticoïdothérapie du lupus érythémateux disséminé

Histoire d'un malade atteint de lupus érythémateux disséminé et de tuberculose pulmonaire intercurrente. Le traitement complet médical et chirurgical des deux affections a été effectué sans qu'ils interfèrent l'un sur l'autre. Le traitement du lupus consistait en petites doses d'entretien de prednisone; les doses étaient augmentées à certains moments lorsqu'une recrudescence des symptômes l'exigeait. Le traitement de la tuberculose a consisté en isoniazide-streptomycine-PAS et alitement, et ensuite, lorsque le moment a été jugé favorable, en résection du lobe supérieur droit détruit.

Le lupus est actuellement en rémission et l'exérèse des lésions tuberculeuses a été favorable, huit cultures de l'expectoration ont été négatives pour le *M. tuberculosis* dans les six mois qui ont suivi la résection.

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Notes

SOME OBSERVATIONS ON THE COMPOSITION OF BACTERIAL POPULATION OF PAS-RESISTANT MYCOBACTERIUM TUBERCULOSIS

Karlson et al.[1] reported that the growth of tubercle bacilli isolated from patients treated by PAS was smaller in medium containing PAS than in medium containing no drug and that the strains isolated were the mixture of PAS-resistant and PAS-susceptible organisms. Nitti and associates[2] reported that PAS-resistant strains of tubercle bacilli were not stable and that reduction of resistance in the strains was produced by transferring them on medium containing no drug. In the previous report, the present writer[3] has reported that the composition of population of PAS-resistant *M. tuberculosis* is heterogeneous and that the heterogeneous bacterial population is not derived from the insufficient selection of the strain but from the nature of the strain itself. The purpose of the present paper is to report some observations on the same problem and some interesting results on the composition of the bacterial population of strains of tubercle bacilli simultaneously resistant to both PAS and streptomycin and that of strains simultaneously resistant to PAS and isoniazid.

Strains: Mycobacterium tuberculosis var. *hominis*, strain Aoyama-B, was used throughout the study.

PAS-resistant strains: A PAS-resistant strain was isolated from the original parent strain by multiple steps of selection and the strain was transferred onto media containing 100 γ of PAS per ml. of medium. The transfer (selection by 100 γ of PAS) was made after every six weeks of incubation. In the following description, the term "P-R" indicates a PAS-resistant strain and "100 γ-*a-transfer*" indicates the number of selection by 100 γ of PAS.

PAS- and streptomycin-resistant strains: A PAS-resistant strain obtained by six transfers onto medium containing 100 γ of PAS (P-R, 100 γ-6-transfers) was selected by transferring it three times onto media containing 500 γ of PAS. This strain is designated as P-R (100 γ-6-transfers and 500 γ-3-transfers). From the strain, a mutant strain resistant to 200 γ of streptomycin was isolated by one step of selection, and the strain isolated was further selected by transferring it onto medium containing 100 γ of PAS and 200 γ of streptomycin in combination. The transfer was made after every six weeks of incubation. In the following description, the term "P-SM-R" indicates a strain simultaneously resistant to PAS and streptomycin and *a-transfers* indicates the number of selection by 100 γ of PAS and 200 γ of streptomycin in combination.

PAS- and isoniazid-resista[illegible]: From the strain P-R (100 γ-6-transfers and 500 γ-3-transfers), a mutant strain [illegible]nt to 10 γ of isoniazid was isolated by one step of selection and the strain isolated was further transferred onto medium containing 100 γ of PAS and 10 γ of isoniazid in combination. The transfer was made after every six weeks of incubation. In the following description, the term "P-IN-R" indicates a strain simultaneously resistant to PAS and isoniazid and "a-transfers" indicates the number of selection by 100 γ of PAS and 10 γ of isoniazid in combination. All cultures were incubated at 37°C.

Medium: Ogawa's medium was used throughout the study. The composition of the medium is as follows: Basal solution (1 per cent sodium glutamate and 1 per cent KH_2PO_4),

[1] KARLSON, A. G., *et al.*: Dis. of Chest, 1949, *16*, 667.
[2] NITTI, V., *et al.*: Arch. tisiol., 1950, *5*, 444.
[3] TSUKAMURA, M.: Am. Rev. Tubere., 1957, *75*, 608.

TABLE 1

COMPOSITION OF BACTERIAL POPULATION OF PAS-RESISTANT STRAINS OF MYCOBACTERIUM TUBERCULOSIS VAR. HOMINIS (STRAIN AOYAMA-B)

Strain	Average of Viable Count Per Tube*			
	PAS 0 γ (Control)	PAS 1 γ	PAS 10 γ	PAS 100 γ
P-R (100 γ-9-transfers)..	79.8 (±9.41)	55.1 (±8.32)	16.7 (±3.72)	13.4 (±2.84)
P-R (100 γ-6-transfers and 500 γ-3-transfers)..	71.1 (±8.11)	51.7 (±8.90)		22.8 (±4.73)
P-R (100 γ-14-transfers).	46.1 (±5.78)	29.3 (±3.93)	33.4 (±6.29)	25.9 (±3.32)
P-R (100 γ-15-transfers).	101.1 (±12.8)	79.0 (±9.39)	78.7 (±11.8)	74.0 (±10.4)

* Arithmetic mean (±95 per cent confidence limit)

TABLE 2

COMPOSITION OF BACTERIAL POPULATION OF STRAINS OF MYCOBACTERIUM TUBERCULOSIS VAR. HOMINIS (STRAIN AOYAMA-B) SIMULTANEOUSLY RESISTANT TO PAS AND STREPTOMYCIN

Strain	Average of Viable Count Per Tube*	
	PAS 0 γ (Control)	PAS 100 γ
P-SM-R (8-transfers)	91.1 (±12.10)	70.3 (±8.27)
P-SM-R (9-transfers)	45.8 (±8.78)	23.5 (±3.22)
P-SM-R (9-transfers)	24.4 (±4.00)	17.2 (±3.09)

* Arithmetic mean (±95 per cent confidence limit)

100 ml.; eggs, 200 ml.; glycerol, 6 ml.; 2 per cent solution of malachite green, 6 ml. Every 8 ml. of medium were poured into tubes and slanted by sterilization at 90°C. for sixty minutes. Streptomycin, isoniazid, and PAS were added prior to sterilization and the activity of the drugs was regarded as unchangeable by sterilization. Dihydrostreptomycin sulfate[4] isoniazid,[5] and sodium para-aminosalicylate[5] were used in the study.

Method of testing the composition of the bacterial population: An appropriate amount of organisms were shaken with glass beads for ten minutes. A cell suspension of approximately 1 mg. per ml. of saline was prepared and allowed to stand for thirty minutes. From the suspension 10^{-4} and 10^{-5} dilutions were prepared and used for testing the composition of the population.

The test consisted of inoculating a series of tubes containing various concentrations of PAS with the same amount of inoculum (0.02 ml. by a large whirled loop). A series of tubes containing no drug was included in each series in order to give a total viable count. The numbers of organisms resistant to the various concentrations were thus determined. Drug concentrations used for the test were 0 (control), 1 γ, 10 γ, and 100 γ of PAS per ml. Calculation of the viable count was performed after four weeks of incubation on medium containing no drug and after six weeks of incubation on medium containing PAS.[3]

The results obtained are shown in tables 1 through 3. As shown in table 1, the composition of bacterial population of the PAS-resistant strain was heterogeneous and the strain contained a considerable number of cells susceptible to 1 γ of PAS even after fifteen transfers onto medium containing 100 γ of PAS. Between the number of cells

[4] Manufactured by Meiji.
[5] Manufactured by Tanabe.

TABLE 3

COMPOSITION OF BACTERIAL POPULATION OF STRAINS OF MYCOBACTERIUM TUBERCULOSIS VAR. HOMINIS (STRAIN AOYAMA-B) SIMULTANEOUSLY RESISTANT TO PAS AND ISONIAZID

Strain	Average of Viable Count Per Tube*	
	PAS 0 γ (Control)	PAS 100 γ
P-IN-R (5-transfers)	21.2 (±4.43)	23.3 (±3.69)
P-IN-R (6-transfers)	54.2 (±14.2)	51.2 (±12.2)
P-IN-R (7-transfers)	93.9 (±17.8)	73.0 (±16.2)
P-IN-R (8-transfers)	19.0 (±5.21)	23.8 (±4.96)

* Arithmetic mean (±95 per cent confidence limit)

grown on medium containing no drug and that on medium containing 1 γ, 10 γ, or 100 γ of PAS, a significant difference was observed. Statistical calculations performed on the basis of the null hypothesis indicated that the difference was highly significant in the level of 95 per cent confidence rate (P = less than 1 per cent).

As shown in table 2, it was also indicated that the composition of population of the strain P-SM-R was heterogeneous with respect to PAS resistance and the strain contained a considerable number of cells susceptible to 100 γ of PAS even after 6 transfers onto medium containing 100 γ of PAS and 3 transfers onto medium containing 500 γ of PAS, and thereafter 9 transfers onto medium containing 100 γ of PAS and 200 γ of streptomycin in combination. The difference between the viable count on medium containing no drug and that on medium containing 100 γ of PAS was highly significant (P = less than 1 per cent) by the test based on the null hypothesis.

As shown in table 3, it was indicated, however, that the composition of the population of the strain P-IN-R was homogeneous and that the strain did not contain any significant number of cells susceptible to 100 γ of PAS. The difference between the viable count on medium containing no drug and that on medium containing 100 γ of PAS was not significant in the level of 95 per cent confidence rate (P = larger than 5 per cent).

* * *

The writer[3] reported previously that the composition of the bacterial population of the PAS-resistant strain of *M. tuberculosis* var. *hominis* is significantly heterogeneous with respect to PAS resistance. Moreover, the heterogeneity is not derived from the insufficient selection of the strain but from the nature of the strain itself. The results obtained in the present paper gave the same results.

The present paper was likewise concerned with the composition of strains of tubercle bacilli simultaneously resistant to both PAS and streptomycin (P-SM-R) and that of strains simultaneously resistant to PAS and isoniazid (P-IN-R). The results obtained indicate that the composition of the population of P-SM-R is heterogeneous and that of P-IN-R is homogeneous with respect to PAS resistance. If one supposed the existence of genes in *M. tuberculosis*, the following considerations would be permitted. If the genes determining PAS resistance, streptomycin resistance, and isoniazid resistance were indifferent to each other, the composition of population with respect to PAS resistance should be the same, i.e., heterogeneous in these two strains P-SM-R and P-IN-R. However, the results indicate that that is homogeneous in the strain P-IN-R. The fact suggests that a specific relationship exists between the genes determining PAS resistance and those determining isoniazid resistance and a marked characteristic in the PAS-resistant strain,

i.e., the heterogeneity of population of the strain, can be changed by the mutation to isoniazid resistance.

Szybalski and associates[6] reported that the mutation rate to PAS and isoniazid resistance simultaneously was larger than the value expected from the mutation rate to PAS resistance alone and that to isoniazid resistance alone in *B. megaterium*.

Tsukamura and co-workers[7] reported that the frequency of mutation to isoniazid resistance in the PAS-resistant strain of *M. tuberculosis* var. *hominis* was somewhat higher than that in the original parent strain and that the frequency of mutation to PAS resistance in the isoniazid-resistant strain was somewhat higher than that in the original parent strain and supposed that a (or several) common gene may exist between the genes determining PAS resistance and those determining isoniazid resistance. The results obtained in the present paper appear to support the previous supposition.

In summary: The composition of a bacterial population in the PAS-resistant strain of *Mycobacterium tuberculosis* var. *hominis* was indicated to be significantly heterogeneous even after repeated selections of the strain. The strain contained a considerable number of cells susceptible to 1 γ of PAS even after fifteen transfers onto medium containing 100 γ of PAS.

The composition of the population in the strains simultaneously resistant to PAS and streptomycin was also heterogeneous with respect to PAS resistance; that in the strains simultaneously resistant to PAS and isoniazid was, however, homogeneous with respect to PAS resistance. The results suggest that a specific relationship exists between the genes determining PAS resistance and those determining isoniazid resistance and that a marked characteristic in the PAS-resistant strain, i.e., the heterogeneity of population, can be changed by the mutation to isoniazid resistance.

Obuso National Sanatorium
Obu, Aichi, Japan

Michio Tsukamura

May 8, 1957

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DRUG-SUSCEPTIBILITY TESTING IN TUBERCULOSIS[1]

A Method Using Diluted Bacterial Suspensions for the Indirect Test

Drug-susceptibility tests are performed by equal inoculation of solid media with and without added drugs. The interpretation is based on a comparison of the amounts of growth appearing on each. A culture is usually considered to be resistant to a particular drug concentration when, after incubation for a specified period, growth on medium containing that concentration approximates the amount of growth on drug-free control slants. Steenken[2] has recommended a refinement of this method by making weekly observations during the incubation period. His procedure takes into account the rapidity of growth in drug and control tubes.

Increasing attention is being given to the size of inoculum in the performance of susceptibility tests. Middlebrook[3] emphasized the importance of this consideration in 1954 by demonstrating that as few as 0.5 per cent of resistant tubercle bacilli in a culture can totally mask the presence of susceptible organisms when a heavy inoculum from a liquid culture is applied to solid medium with and without added drugs. Kenney and associates[4] also demonstrated that the size of inoculum plays a critical role in determining the proportion of resistant bacilli present in a culture.

Various dilutions of bacterial suspensions have been employed for the indirect test. Woolley[5] used suspensions sufficiently diluted to produce distinctly isolated colonies on drug-free medium controls. The Fitzsimons Army Hospital group,[6] in a modification of the method devised by Middlebrook,[7] recommended suspensions diluted sufficiently to yield from 50 to 100 colonies on the controls. Bogen[8] used suspensions which resulted in almost but not quite confluent growth on drug-free medium. The 1956 revision of *Tuberculosis Laboratory Methods*[9] recommended suspensions of slightly less density than a barium sulfate standard No. 1 with results to be read after three to four weeks' incubation; the test to be acceptable whenever 3-plus to 4-plus growth (almost confluent to confluent) appears on the controls.

A modified method of preparing and diluting suspensions of *M. tuberculosis* has been used in this and other laboratories of the Florida Tuberculosis Hospital System for the past year. As used in this laboratory, the technique avoids the errors which are inherent in the use of variable and heavy inocula. The purpose of this report is to describe the method and record the results obtained.

[1] This research was supported in part by the United States Air Force under Contract No. AF 41(657)-26; monitored by the United States Air Force School of Aviation Medicine, Randolph Field, Texas.

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[3] MIDDLEBROOK, G.: Am. Rev. Tubere., 1954, *70*, 922.

[4] KENNEY, M., *et al.*: Am. Rev. Tubere., 1955, *72*, 390.

[5] WOOLLEY, J. S.: Personal communication, 1956.

[6] MORSE, W. C., *et al.*: Research and Development Service, Fitzsimons Army Hospital, Report No. 1, May 27, 1955.

[7] MIDDLEBROOK, G., *et al.*: Am. Rev. Tubere., 1954, *70*, 852.

[8] BOGEN, E.: Tr. Fourteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, and Navy, 1955, p. 248.

[9] RUNYON, E. H., *et al.*: Tuberculosis Laboratory Methods, as revised following the Fifteenth Conference on the Chemotherapy of Tuberculosis. Veterans Administration, Army, and Navy, 1956, p. 551.

Wood applicator sticks cut with a one-quarter inch flat taper at one end were autoclaved in 16 by 150 mm. screw cap tubes, 5 sticks per tube.

Difco TB broth without Tween® or albumin was dispensed in 2.0 ml. amounts in 13 by 100 mm. test tubes, plugged lightly with No. 2 corks, covered in sets of 10 tubes with heavy paper, and autoclaved. Following sterilization the corks were pushed firmly into the tubes.

Serologic pipettes, 1.0 ml. graduated in 1/100ths, were cut at the 0.2 ml. line and fitted with 2.0 ml. rubber bulbs. Pipettes were then placed in sets of 10 in glass jars 6 to 7 inches deep, covered with heavy paper, and autoclaved.

The working standard for estimating turbidity of bacterial suspensions prior to final dilution consisted of a 1:5 dilution of barium sulfate standard No. 1.

Löwenstein-Jensen medium with and without added drugs was dispensed in 7.0 ml. amounts in flat 1-ounce prescription bottles. Drug concentrations used were streptomycin, 10 and 100 γ per ml.; para-aminosalicylic acid (PAS), 10 and 100 γ per ml.; and isoniazid, 1.0 and 5 γ per ml.

All of the above materials were prepared in advance. They were dispensed in the numbers stated to provide for the performance of 10 susceptibility tests at one time. With the materials at hand one person can easily prepare 10 suspensions and inoculate the 60 drug slants and the 20 controls in less than two hours.

Primary growth on Löwenstein-Jensen medium was removed with a sterile applicator "spade," care being taken to collect portions of growth from various areas of the slant. Colonies were thus transferred to a tube of broth and triturated against the side of the tube in small amounts of liquid. At least three "spadefuls" were used when growth was sufficient in order to obtain representative sampling.

The bacterial suspension was then allowed to stand for about thirty minutes to permit settling of visible clumps. Using a pipette fitted with a bulb, just enough of the supernatant suspension was transferred to a second tube of broth to obtain a very faint turbidity approximating that of the working standard. This suspension was then mixed well (but carefully to avoid aerosol formation), after which 0.2 ml. was transferred to a third tube of broth. Thus, the final suspension was a 1:10 dilution of a faintly visible bacterial suspension.

When only one or two colonies were available for testing, a suspension was prepared in approximately 1.0 ml. of broth. If the resulting suspension was clear, there was no further dilution. The tube was allowed to stand as usual to permit settling of any macroscopic clumps. The supernatant suspension was then transferred to an empty sterile tube and was the inoculum used.

Inoculation of media slants was accomplished by spreading 0.05 ml. of the final suspension evenly and very lightly over the entire surface of each slant, using the pipette for this purpose. The same pipette was used throughout. A drug-free control slant was inoculated both at the beginning and at the end of each susceptibility test set. All of these operations were performed in a hood. The media bottles were placed in a horizontal position and left at room temperature overnight to ensure even settling of bacilli onto the surfaces of the slants. The following day the bottles were placed upright and transferred to the incubator.

The first 1,525 tests were incubated for five weeks before reading. Later trials indicated that a four-week incubation period was sufficient for the majority of the tests. This shorter incubation time is being used at present.

The amounts of growth on the drug-free controls of two series of susceptibility tests are shown in table 1. Of the initial 1,525 tests, inoculated as described and incubated for five weeks, 349 (22.9 per cent) revealed 4-plus growth (confluent). In the next 407 tests the same size of inoculum was used, but the incubation period was reduced to four weeks. Of this group of tests, 54 (13.3 per cent) yielded 4-plus growth on the control slants.

It will be noted from the table that the proportion with 4-plus growth decreased with the shorter incubation period; whereas, the per cent with growth of less than 3-plus remained essentially the same as in the first series.

TABLE 1

AMOUNTS OF GROWTHS ON DRUG-FREE CONTROLS OF 1,932 CONSECUTIVE SUSCEPTIBILITY TESTS INOCULATED AS DESCRIBED

Reading*	Tests Incubated at 5 Weeks		Tests Incubated at 4 Weeks	
	Number	Per Cent	Number	Per Cent
4+ growth	349	22.9	54	13.3
3+ growth	935	61.3	292	71.7
2+ growth	116	7.6	34	8.4
1+ growth	76	5.0	14	3.4
Less than 1+ growth	43	2.8	9	2.2
Contaminated	6	0.4	4	1.0
Totals	1,525	100.0	407	100.0

* Less than 50 colonies ..... actual colony count
50 to 200 colonies ..... 1+
Innumerable discrete colonies ..... 2+
Not quite confluent growth ..... 3+
Confluent growth ..... 4+

TABLE 2

COMPARISONS BETWEEN PERCENTAGES OF TESTS REVEALING CONFLUENT GROWTH ON DRUG-FREE CONTROLS AND CONFLUENT GROWTH ON DRUG-CONTAINING MEDIA

Medium	First Series of Tests*		Second Series of Tests†	
	Number	Per Cent	Number	Per Cent
Drug-free medium	349	22.90	54	13.3
Streptomycin, 10 γ per ml.	65	4.30	16	3.9
Streptomycin, 100 γ per ml.	24	1.60	7	1.7
PAS, 10 γ per ml.	5	0.30	3	0.7
PAS, 100 γ per ml.	1	0.06	1	0.2
Isoniazid, 1 γ per ml.	80	5.20	22	5.4
Isoniazid, 5 γ per ml.	42	2.70	15	3.7

* 1,525 drug-susceptibility tests
† 407 drug-susceptibility tests

Significant discrepancies between amounts of growth on the two control bottles in each test were seldom observed.

The percentages of confluent growths (4-plus) on media with and without added drugs are shown in table 2. It will be noted that with each drug concentration this percentage was well below that of similar growth amounts on drug-free controls, since many of the latter accompanied drug-susceptible, or partially resistant, cultures.

The amounts of growth yielded on medium containing 100 γ of streptomycin per ml. by 81 cultures producing confluent growth both on 10 γ of streptomycin per ml. and on drug-free controls are listed in table 3. It will be noted that in the first series of tests, 65 cultures revealed confluent growth on medium containing 10 γ of streptomycin per ml. and 24 (36.9 per cent) of these 65 cultures also revealed confluent growth on 100 γ of

TABLE 3

AMOUNTS OF GROWTH YIELDED ON MEDIUM CONTAINING 100 γ OF STREPTOMYCIN PER ML. BY CULTURES PRODUCING CONFLUENT GROWTH ON MEDIUM CONTAINING 10 γ OF STREPTOMYCIN PER ML.

Amounts of Growth* on Streptomycin, 10 γ per Ml.	Amounts of Growth on Streptomycin, 100 γ per Ml.	First Series of Tests†		Second Series of Tests‡	
		Number	Per Cent	Number	Per Cent
4+ on all	4+	24	36.9	7	43.8
	3+	16	24.6	3	18.8
	2+	8	12.3	2	12.5
	1+	8	12.3	2	12.5
	less than 1+	5	7.7	1	6.2
	0	4	6.2	1	6.2
Totals		65	100.0	16	100.0

* *See* footnote to table 1
† *See* footnote * to table 2
‡ *See* footnote † to table 2

TABLE 4

AMOUNTS OF GROWTH YIELDED ON MEDIUM CONTAINING 5 γ OF ISONIAZID PER ML. BY CULTURES PRODUCING CONFLUENT GROWTH ON MEDIUM CONTAINING 1 γ OF ISONIAZID PER ML.

Amounts of Growth* on Isoniazid, 1 γ per Ml.	Amounts of Growth on Isoniazid, 5 γ per Ml.	First Series of Tests†		Second Series of Tests‡	
		Number	Per Cent	Number	Per Cent
4+ on all	4+	42	52.5	15	68.2
	3+	11	13.8	3	13.6
	2+	4	5.0	0	0.0
	1+	2	2.5	0	0.0
	less than 1+	16	20.0	0	0.0
	0	5	6.2	4	18.2
Totals		80	100.0	22	100.0

* *See* footnote to table 1
† *See* footnote * to table 2
‡ *See* footnote † to table 2

streptomycin per ml. A total of 48 (73.8 per cent) of these 65 cultures revealed from 2-plus to 4-plus growth on this concentration. Only 4 (6.2 per cent) cultures failed to produce growth on medium containing 100 γ of streptomycin per ml.

Since the main objective in employing the size of inoculum described herein has been to permit valid comparisons between amounts of growth on media with and without added drugs, these results are considered significant. Middlebrook[10] has demonstrated that there is a decreasing incidence of streptomycin-resistant variants with increasing concentra-

[10] MIDDLEBROOK, G.: Am. Rev. Tubere., 1952, *65*, 765.

tions of streptomycin. This would seem to indicate that a culture containing large numbers of tubercle bacilli resistant to 100 γ of streptomycin per ml. would usually contain an even greater number of organisms resistant to 10 γ of streptomycin per ml. On this basis it is believed that valid comparisons, in terms of drug-resistant tubercle bacilli actually present, were possible in the majority of these 65 tests. As this table illustrates, similar findings occurred in the second series of tests.

The amounts of growth yielded on medium containing 5 γ of isoniazid per ml. by 102 cultures producing confluent growth on 1 γ of isoniazid per ml. and on drug-free controls are listed in table 4. It may be noted that 42 (52.5 per cent) of the 80 tests in the first series which resulted in confluent growth on 1 γ of isoniazid per ml. also resulted in confluent growth on the higher concentration of isoniazid; while a total of 57 (71.3 per cent) of these 80 cultures produced from 2-plus to 4-plus growth on this concentration. Results of the second series of tests revealed that the majority of these 22 cultures likewise produced from 2-plus to 4-plus growth on 5 γ of isoniazid per ml.

Reports of individual cultures containing tubercle bacilli resistant to various concentrations of isoniazid frequently appear in the literature. A bacterial population study by Peizer and Widelock[11] revealed that many of their cultures contained descending numbers of isoniazid-resistant mutants as drug concentrations increased. Cultures containing large numbers of organisms resistant to 5 γ of isoniazid per ml. often contained even greater numbers of bacilli resistant to the 1 γ per ml. concentration of the drug.

Population studies were not conducted on the cultures listed in table 4 which produced confluent growth. For the reason stated above, however, interpretation difficulties were not encountered.

Tests revealing confluent growth on medium containing 10 γ of PAS per ml. were too few in number to warrant separate tabulation here. However, 5 of the 8 cultures listed in table 2 as producing confluent growth on medium containing 10 γ of PAS per ml. yielded from 2-plus to 4-plus growth on medium containing 100 γ of PAS per ml. The relatively low mutation rate of tubercle bacilli to PAS resistance, as compared to that of streptomycin and isoniazid, would seem to discount the possibility that invalid interpretations, in terms of significant PAS resistance, were made from the results of these tests.

* * *

Drug-susceptibility tests may provide misleading information unless several important considerations are kept in mind. It cannot be assumed that the ratio of drug-resistant to drug-susceptible organisms obtained from indirect susceptibility tests necessarily reflects that occurring *in vivo* because of the differences in growth rate between the two during subculture of the original isolate.

The presence of a relatively low proportion of drug-resistant organisms in a bacterial suspension can produce confluent growth on drug-containing media and thus mask the presence of significant numbers of drug-susceptible organisms, if too heavy an inoculum is used.[3] With the size of inoculum used in the tests described here this error was avoided.

Reduction of the incubation period to four weeks further increased the quantitative value of the tests. It is quite possible that with the size of inoculum used for the tests reported here results could be reported at the end of three weeks' incubation in most instances. Preliminary observations indicate that many of the present tests reveal 3 plus growth on drug-free controls by the end of the third week of incubation. The procedures given in *Tuberculosis Laboratory Methods*[9] take into account the fact that some drug-resistant tubercle bacilli grow at a slower rate than drug-susceptible bacilli. However,

[11] Peizer, L. R. and Widelock, D.: Am. Rev. Tubere., 1955, *72*, 246.

significant proportions of drug-resistant organisms, when present, will usually appear by the time 3-plus growth occurs on the controls.

In summary: A modified method of preparing and diluting suspensions of tubercle bacilli for the indirect susceptibility test on Löwenstein-Jensen medium has been described. The results obtained indicated that with the size of inoculum used it was possible to obtain a valid comparison between the amount of growth appearing on media with and without added drugs.

CENTRAL TUBERCULOSIS LABORATORY
SOUTHWEST FLORIDA TUBERCULOSIS HOSPITAL
TAMPA, FLORIDA, AND

FRANK P. DUNBAR
REYNOLDS DAVIS[12]
MILDRED B. JEFFERIES

BUREAU OF LABORATORIES
FLORIDA STATE BOARD OF HEALTH
JACKSONVILLE, FLORIDA

June 21, 1957

[12] Deceased.

THE SELECTIVE ACTIVITY OF FLUID THIOGLYCOLLATE MEDIUM FOR GROUP DIFFERENTIATION OF ATYPICAL CHROMOGENIC MYCOBACTERIA, MYCOBACTERIUM TUBERCULOSIS, AND SAPROPHYTIC MYCOBACTERIA

Reports of human infections caused by atypical chromogenic mycobacteria have become more numerous recently.[1-10] Since these acid-fast bacilli are frequently encountered in the tuberculosis laboratory and since they have some characteristics unlike human tubercle bacilli and others unlike the saprophytic mycobacteria, it would be well to know whether or not they possess a biochemical characteristic that would define them as a group. Tarshis and Frisch[11] reported they were able to cultivate atypical strains in thioglycollate broth and that slow development and poor growth were characteristics peculiar to these strains. On the other hand, the medium failed to support the growth of true tubercle bacilli, but supported rapid and luxurious growth of saprophytic strains. On the basis of these interesting observations, the present writers decided to investigate further the differential potentiality of this medium and at the same time to test the ability of the atypical strains to form serpentine cords, bind neutral red, and produce catalase.

One hundred strains of atypical mycobacteria and 10 strains of human tubercle bacilli were included in this study. The latter served as controls. All of the strains were recovered in the laboratory from various sources of clinical material, cultured for *M. tuberculosis*, which was obtained from patients on the Tuberculosis Service, on the Non-Tuberculous Chest Service, and on the Urological Service. Fourteen strains of the former group were photochromogens of which 8 were recovered from gastric washings, 5 from sputum, and one from kidney urine. The remaining 86 strains were scotochromogens, 37 of which were recovered from gastric washings, 28 from sputum, 9 from kidney urine, 5 from bronchial washings, 4 from pleural fluids, 2 from lung tissue removed at autopsy, and one from material obtained from a chronic leg ulcer.

The sodium hydroxide method was used for concentration of specimens. Smear preparations were stained by the Ziehl-Neelsen technique. Each specimen was inoculated on duplicate tubes of Löwenstein-Jensen and Petragnani media. The cultures were incubated at 37°C. and were examined weekly for a period of eight weeks. Fluid thioglycollate medium (B-B-L) was used exclusively throughout this study, and inoculations were made by transferring several colonies from respective Löwenstein-Jensen and/or Petragnani cultures. Incubation was at 37°C. and daily observations were made whenever possible. The ability of the specimens to form cords was determined by microscopic examination of stained smear preparations of seven-day-old cultures in Bacto-Dubos broth containing Bacto-Dubos

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[1] Wolinsky, E., *et al.*: Am. Rev. Tuberc., 1957, *75*, 180.

[2] Buhler, V. A., and Pollak, A.: Am. J. Clin. Path., 1953, *23*, 363.

[3] Timple, A., and Runyon, E. H.: J. Lab. and Clin. Med., 1954, *44*, 202.

[4] Hall, W. H., and Erlandson, H.: Tr. Thirteenth Conference on Chemotherapy of Tuberculosis, Veterans Administration, Army, and Navy, 1954, p. 224.

[5] Young, R. D.: Lancet, 1955, *2*, 750.

[6] Weed, L. A., *et al.*: Proc. Staff Meet., Mayo Clin., 1956, *31*, 238.

[7] Weed, L. A., *et al.*: Proc. Staff Meet., Mayo Clin., 1956, *31*, 246.

[8] Wood, L. E., *et al.*: Am. Rev. Tuberc., 1956, *73*, 917.

[9] Crow, H. E., *et al.*: Am. Rev. Tuberc., 1957, *75*, 199.

[10] Koch, M. L.: Pub. Health Rep., 1956, *71*, 910.

[11] Tarshis, M. S., and Frisch, A. W.: Am. Rev. Tuberc., 1952, *65*, 278.

medium albumin (Difco). The method of Middlebrook and Dubos[12] was used for determination of binding of neutral red. The method described in "Tuberculosis Laboratory Methods"[13] was used for demonstration of catalase activity.

Microscopic examination of stained smear preparations of Löwenstein-Jensen or Petragnani cultures showed that all of the atypical strains were acid fast; however, there was considerable variation in the intensity of staining. Three morphologic types were distinguishable: (*1*) those resembling true tubercle bacilli (4/14 photochromogens and 22/86 scotochromogens); (*2*) those in which the cells were longer and thicker than in the former, appearing to be heavily beaded (9/14 and 45/86); and (*3*) those in which the cells were very small and solid staining (1/14 and 19/86). All of the strains of tubercle bacilli were tinctorially and morphologically typical of *M. tuberculosis* var. *hominis*.

Fluid thioglycollate medium supported the growth of 91 per cent of the atypical strains (11 photochromogens and 80 scotochromogens), but failed to support the growth of tubercle bacilli. The development and growth of the former strains were characteristically slow and poor and were confined to the aerobic portion of the culture medium. Prolonged incubation did no more than slightly enhance the extent of growth, from plus to 2-plus. Seven to twenty-one days were required for initial growth of the photochromogens and fourteen to forty-two days for the scotochromogens.

Two distinct patterns of growth were associated with cultivation in thioglycollate broth. One, referred to as the "cord pattern" (and most frequently encountered), was characterized by enlargement of the inoculated colonies with subsequent development of a very slimy appearance. Upon shaking, long mucoid threads (or cords) extended from, but remained attached to, the mother-colony. The other, referred to as the "weblike pattern" was characterized by the development of a delicate weblike growth covering the surface of the medium. Six strains of photochromogens and 46 strains of scotochromogens developed the "cord pattern" of growth, whereas 5 and 34 strains, respectively, developed the latter pattern. No correlation could be demonstrated between morphologic type and thioglycollate growth pattern; however, in most instances growth in thioglycollate broth was accompanied by considerable change in the morphologic appearance. The predominant change was one of pleomorphism with the cells appearing as long, filamentous, granular bacilli, which retained their acid-fast property but showed variations in intensity of staining.

All atypical strains failed to form cords and bind neutral red. On the other hand, all of them showed strong catalase activity. The strains of tubercle bacilli examined gave positive results with all 3 of the tests.

In summary: From the results of this study it is evident that fluid thioglycollate medium (B-B-L) will support the growth of most strains of atypical mycobacteria in a manner characteristic of these organisms. This medium will not support the growth of tubercle bacilli. Therefore, on the basis of this report and the previous report of Tarshis and Frisch,[11] it is logical to conclude that thioglycollate broth may be used as a selective medium for *group* differentiation of the atypical mycobacteria, *M. tuberculosis*, and the saprophytic mycobacteria.

In retrospect, it is well to remember that many strains of atypical acid-fast bacilli morphologically resemble tubercle bacilli, and this similarity applies to bacilli present in clinical material as well as to those growing on Löwenstein-Jensen and Petragnani

[12] Middlebrook, G., and Dubos, R. J.: Am. Rev. Tuberc., 1948, *58*, 583.

[13] Tuberculosis Laboratory Methods: Tr. Fifteenth Conference on Chemotherapy of Tuberculosis, Veterans Administration Army and Navy, 1956, p. 559.

media. Furthermore, colonial morphology may also present a problem. It is not difficult to confuse cultures of photochromogens (those usually associated with human disease) with cultures of saprophytic strains, and occasionally one may encounter a culture that could be mistaken for that of true tubercle bacilli. Therefore, in order to avoid danger of misinterpretation, it would be advantageous to study further all "doubtful" cultures by inoculation into thioglycollate broth.

CLINICAL LABORATORIES
VETERANS ADMINISTRATION CENTER
WOOD, WISCONSIN, AND

MARIE L. KOCH
VIRGINIA L. GRIFFIN
EARL E. AGOSTINI

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
MARQUETTE UNIVERSITY SCHOOL OF MEDICINE
MILWAUKEE, WISCONSIN

July 16, 1957

CHILDHOOD MILIARY AND MENINGEAL TUBERCULOSIS IN NEW YORK CITY

The U. S. Public Health Service is currently investigating the usefulness of isoniazid in the prevention of miliary and meningeal involvement in children with asymptomatic primary tuberculosis.[1] It must be recognized, however, that no matter how effective the drug may be, its usefulness in the prevention of miliary and meningeal tuberculosis is dependent on the identification and treatment of the susceptible children prior to widespread dissemination. In this connection, it was considered worth while to investigate whether or not the children in New York City currently being registered as having miliary or meningeal tuberculosis could have benefited from such preventive use of isoniazid.

Records were reviewed of all children less than ten years of age who were registered at the Bureau of Tuberculosis, New York City, as having bacteriologically confirmed, newly diagnosed miliary or meningeal tuberculosis during 1956. In a total of 21 children these criteria were fulfilled. In table 1 may be seen the essential information for the 21 cases. Only 2 of the children in this series were white; 13 were three years of age or less.

The probable source case was found in only 10 instances (slightly less than 50 per cent of the cases), in spite of all the usual public health measures which were taken in an attempt to identify the source of infection. The source case was known *prior* to the diagnosis of miliary or meningeal tuberculosis in the affected child in 5 instances, and discovered *after* the diagnosis was made in 5 instances.

In the 5 instances in which the contacts to a known source case were not examined prior to dissemination (due to poor family cooperation or faulty medical supervision), the early use of isoniazid might have prevented the development of miliary or meningeal tuberculosis. In the 11 instances in which no source case was found, the family contacts were examined and found to be free of active tuberculosis in 8 instances. In the remaining 3, the family was either uncooperative or unable to be traced.

In no instance did clinical evidence of the tuberculous dissemination become evident while a child was under medical supervision either as a contact to an infectious case of tuberculosis, or because of a positive tuberculin reaction or an abnormal finding on the chest roentgenogram. In 8 children, roentgenographic or bacteriologic evidence of intrathoracic tuberculosis was found in addition to the miliary or meningeal involvement, but this was discovered only after the child already had clinical evidence of hematogenous dissemination.

In all instances, the children presented themselves with the symptoms of an undiagnosed disease at a general hospital, with variable and, at times considerable, periods of delay from the time of admission to the time the diagnosis was established.

Six of the 21 children studied died, 4 within one month, one within two and one-half months, and one five months after hospital admission. In 3 instances, tuberculous meningitis caused serious permanent nervous system defects, while in the remaining 12 the tuberculous disease had improved or was improving with no noticeable residua.

Miliary and meningeal tuberculosis is not a common problem currently among the children of New York City. Moreover, the evidence collected in this study strongly suggests that in New York City, at any rate, there would be very little opportunity to *prevent* the present occurrence of such cases by the use of isoniazid during the asymptomatic

[1] FEREBEE, S. H., *et al.*: U. S. Public Health Service Tuberculosis Prophylaxis Trials, A Report on a Beginning, presented at the annual meeting of the National Tuberculosis Association, Kansas City, Missouri, May 6, 1957.

TABLE 1

TWENTY-ONE NEW CASES OF MILIARY AND MENINGEAL TUBERCULOSIS REPORTED DURING 1956 IN PERSONS LESS THAN TEN YEARS OF AGE

Bureau of Tuberculosis—New York City

Patient	Characteristics			Source of Infection			Other Tuberculous Disease	Hospital Admission for Miliary or Meningeal Tuberculosis	Final Diagnosis	Outcome
	Age	Sex	Race or Geographic Origin	Relation	Duration of Tuberculosis Known	Type of Supervision				
								date		
1. D. B.	6 months	Female	Negro	Mother	6 months	Private physician	None	4/18/56	Meningitis	Died 4/25/56
2. C. D.	7 months	Male	Negro	Mother	Discovered after diagnosis		None	4/14/56	Miliary tuberculosis	Died 4/26/56
3. O. C.	2¾ years	Male	Puerto Rican	Family not located			None	7/11/56	Miliary tuberculosis	Died 7/26/56
4. J. E.	5½ years	Female	Negro	Father	Discovered after diagnosis		None	1/20/56	Meningitis	Died 2/21/56
5. O. V.	7½ years	Female	Puerto Rican	No information			None	3/4/56	Meningitis	Died 5/16/56
6. M. M.	2¾ years	Female	Puerto Rican	Aunt	More than 1 year	Hospital	Tuberculous meningitis and pneumonia; diagnosed 1/10/56	1/10/56	Tuberculous meningitis and pneumonia	Died 6/1/56
7. L. H.	4 years	Female	Chinese	All family contacts negative			None	4/18/56	Miliary tuberculosis	Cured

8. R. H.	1 year	Male	Negro	Uncle	1 year	Hospital	Gastric culture positive for tuberculosis	8/23/56	Meningitis	Cured
9. M. A.	4½ years	Male	Puerto Rican	All family contacts negative			None	1/24/56	Meningitis	Blind-deaf; still hospitalized
10. A. B.	5 years	Male	White	All family contacts negative			None	7/17/55	Meningitis	Cured
11. A. C.	1½ years	Female	Puerto Rican	Grandfather	2 months	Chest clinic	None; twin has primary tuberculosis	8/24/56	Miliary tuberculosis and meningitis	Improved; still hospitalized
12. C. D.	1 year	Female	Negro	Family uncooperative			Pulmonary tuberculosis; discovered on hospital admission	7/27/56	Meningitis	Improved; still hospitalized
13. A. E.	1 year	Male	Negro	All family contacts negative			Hilar adenitis; discovered on hospital admission	4/4/56	Miliary tuberculosis	Improved; still hospitalized
14. S. G.	2¾ years	Female	Negro	Aunt	4 months	Hospital	Hilar adenitis; discovered on hospital admission	5/9/56	Miliary tuberculosis and meningitis	Left with hemiparesis
15. C. H.	5½ years	Male	Negro	All family contacts negative			Renal tuberculosis; discovered after hospital admission	9/22/56	Meningitis	Improved
16. J. M.	3½ years	Male	White	Mother	Discovered after diagnosis		None	1/15/56	Meningitis	Cured

TABLE 1—CONTINUED

Patient	Characteristics			Source of Infection			Other Tuberculous Disease	Hospital Admission for Miliary or Meningeal Tuberculosis	Final Diagnosis	Outcome
	Age	Sex	Race or Geographic Origin	Relation	Duration of Tuberculosis Known	Type of Supervision		*date*		
17. S. M.	7 months	Female	Puerto Rican	All family contacts negative			None	2/11/56	Miliary tuberculosis	Cured
18. L. M.	6 years	Male	Negro	Grandmother	Many years	Lives in Suffolk County	None	6/14/56	Meningitis	Improved; still hospitalized
19. V. N.	7 months	Male	Puerto Rican	Aunt	Discovered after diagnosis		Pulmonary tuberculosis; discovered after hospital admission	4/28/56	Miliary tuberculosis	Miliary tuberculosis cured; inactive pulmonary tuberculosis
20. H. W.	1 year	Male	Negro	All family contacts negative			Hilar adenitis; discovered on hospital admission			Improved; still hospitalized
21. L. T.	5½ years	Male	Negro	All family contacts negative			Hilar adenitis; discovered on hospital admission	7/15/55	Meningitis	Very extensive and permanent damage to the central nervous system

phase of infection. The present writers do not mean to imply that the development of miliary or meningeal tuberculosis might not be prevented in some instances by the routine use of isoniazid in children with asymptomatic primary tuberculosis. In an urban community like New York City, however, it is unlikely that the "prophylactic" use of isoniazid in children with asymptomatic tuberculous infection can play the major role in eliminating the present small "hard core" of the problem.

Of much more importance than the "prophylactic" use of isoniazid in children to prevent serious forms of childhood tuberculosis is the prompt *discovery* and *treatment* of the source and potential source cases in the community. It is primarily because this aspect of tuberculosis control was emphasized that the new case rate for miliary and meningeal tuberculosis in children less than fifteen years of age in New York City has fallen from 4.5 cases per 100,000 at risk in 1953 to 1.5 cases per 100,000 in 1956. The use of isoniazid in children with asymptomatic as well as symptomatic forms of primary tuberculosis during these years may have made a minor contribution to this decline.

Obviously, the threat of miliary and meningeal tuberculosis will remain so long as sources of infection remain in the community. In New York City, using present techniques, only about 50 per cent of the source cases of the present series of children with miliary and meningeal tuberculosis were discovered. Moreover, the difficulties encountered in detecting the source cases of children with only a positive tuberculin reaction or even clinically evident primary tuberculosis are very much greater. It is clear, therefore, that the development of better techniques for the tracking down and the prompt, effective treatment of all infectious cases of tuberculosis in large urban centers such as New York City is urgently needed if the residual problem of childhood tuberculosis is to be eliminated. As a supplemental measure, BCG vaccination of infants in susceptible population groups prior to infection, in addition to drug therapy after infection has been clinically demonstrated, would seem more logical than reliance on preventive drug therapy alone.

In summary: The 21 cases of miliary and meningeal tuberculosis in children registered in New York City during 1956 are reviewed. In all instances, clinical evidence of hematogenous dissemination was already present at the time the patient first came under medical supervision. It is concluded that these serious forms of childhood tuberculosis, which at present constitute a numerically minor, although still important, threat in New York City, are more likely to be eliminated by emphasis on better case finding and the prompt treatment of all infectious cases than the preventive use of isoniazid in children with asymptomatic primary tuberculosis.

Bureau of Tuberculosis
Department of Health
125 Worth Street
New York 13, N. Y.

Aaron D. Chaves
Arthur B. Robins
Hans Abeles

August 6, 1957

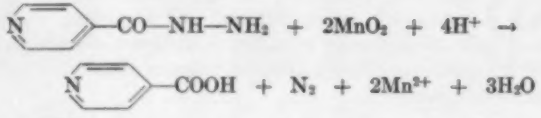
ISONICOTINIC ACID HYPOTHESIS OF THE ANTITUBERCULOUS ACTION OF ISONIAZID

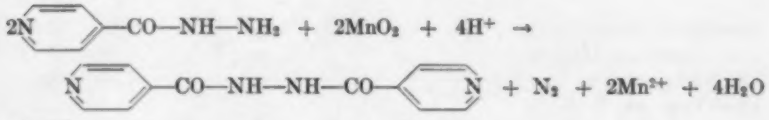
Winder[1] and Tirunarayanan and Vischer[2] recently proposed two slightly differing hypotheses on the mode of action of isoniazid. In both of these, hydrogen peroxide (or other oxidation products of isoniazid) is assumed to be responsible for the inhibition of multiplication of tubercle bacilli. Because of the relatively low susceptibility of tubercle bacilli to hydrogen peroxide, Winder[1] was led to assume that small concentrations of isoniazid give rise to high local concentrations of peroxide within the bacteria in special peroxide-susceptible areas. Tirunarayanan and Vischer[2] gave no explanation for the discrepancy in the minimal inhibition concentration of hydrogen peroxide (10 to 100 γ per ml.[3]) and of isoniazid (0.01 to 0.1 γ per ml.). Despite this discrepancy, it might be suggested that the final antibacterial effect of isoniazid is attributable to hydrogen peroxide set free in consequence of the interaction of isoniazid with the bacterial metabolism, since some potent isoniazid antagonists, e.g., hemin chloride, catalase, sodium pyruvate, and α-ketoglutarate, are hydrogen peroxide destroyers.

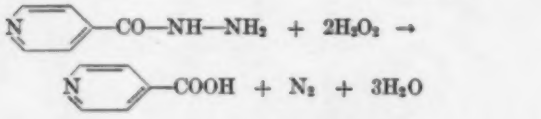
In Winder's description there is no evidence that the hydrogen of the hydrogen peroxide derives from isoniazid. Therefore, another explanation of the result of Winder's experiment will be proposed.[4] Isoniazid was found to be destroyed slowly in water and vigorously in hydrochloric acid by mangan dioxide. Reaction products are nitrogen, N,HN′-diisonicotinoyl-hydrazine, and isonicotinic acid. The real oxidant of isoniazid therefore is probably the Mn^{4+} ion. As it is known (Abel[5]) that Mn^{4+} and hydrogen peroxide react to give rise to Mn^{2+}, oxygen, and hydrogen ion, the inverse reaction is proposed to explain Winder's detection of hydrogen peroxide in the reaction of isoniazid with oxygen and catalytic amounts of manganous chloride. The following five equations may account for the reaction course:

(*1*) $Mn^{2+} + 2OH^- \rightarrow Mn(OH)_2$

(*2*) $Mn(OH)_2 + O_2 \rightleftharpoons MnO_2 + H_2O_2$

(*3*) 

(*4*) 

(*5*) 

[1] WINDER, F.: Am. Rev. Tuberc., 1956, *73*, 779.
[2] TIRUNARAYANAN, M. O., AND VISCHER, W. A.: Naturwiss., 1957, *44*, 11.
[3] BÖNICKE, R.: Naturwiss., 1954, *41*, 577.
[4] In collaboration with Ellen Wempe.
[5] ABEL, E.: Mh. Chem., 1955, *86*, 952.

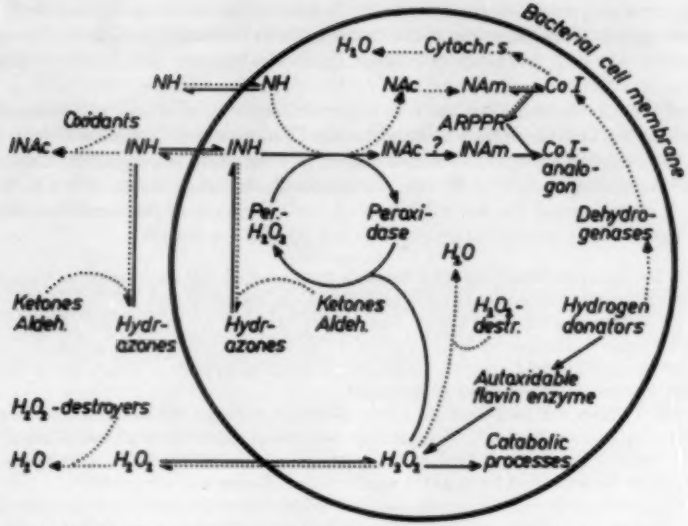


FIG. 1. Isonicotinic acid hypothesis of the antituberculous action of isoniazid.

——▶ Reactions resulting in metabolic lesions by hydrogen peroxide.
. . . .▶ Reactions counteracting the metabolic lesions by hydrogen peroxide.

INH = isoniazid	NH = nicotinoyl-hydrazine
INAc = isonicotinic acid	NAc = nicotinic acid
INAm = isonicotinamide	NAm = nicotinamide
Co I = coenzyme I	ARPPR = adenosine-diphosphoric acid ribose
Cytochr. s. = cytochrome system	Per.-H_2O_2 = peroxidase-H_2O_2-complex
Aldeh. = aldehydes	H_2O_2-destr. = H_2O_2-destroyers

In the reactions (*1*), (*2*), and (*3*), 2 mol of hydrogen peroxide should be formed during the oxidation of 1 mol of isoniazid. Winder[1] observed the formation of only 0.75 mol of peroxide per mol of oxidized isoniazid. This may be explained by the reactions (*4*) and (*5*). Possibly reaction (*3*) has by-reactions, for traces of ammonia have been found in the reaction mixture. According to Lewin and Hirsch,[6] the reaction (*5*) occurs only in the presence of catalysts, such as heavy metals or hemin chloride. In the reactions (*1*) to (*3*) isoniazid presumably may be exchanged by other oxidable substances, which would explain the finding by Barry and associates[7] of hydrogen peroxide in autoclaved Proskauer and Beck culture medium containing traces of manganous ion.

Three other hypotheses for the mode of action of isoniazid by Nitti and Curci,[8] Knox[9] and Maher and associates[10] also assume hydrogen peroxide to be the final cause of antibacterial action of isoniazid. In these hypotheses isoniazid is supposed to block the removal of hydrogen peroxide produced by the tubercle bacilli themselves. These hypotheses do not

[6] LEWIN, E., AND HIRSCH, J. G.: Am. Rev. Tubere., 1955, *71*, 732.
[7] BARRY, V. C., *et al.*: Am. Rev. Tubere., 1957, *75*, 476.
[8] NITTI, V., AND CURCI, G.: Arch. tisiol., 1953, *8*, 859.
[9] KNOX, R.: J. Gen. Microbiol., 1955, *12*, 191.
[10] MAHER, J. R., *et al.*: Am. Rev. Tubere., 1957, *75*, 517.

explain the strong antagonism of nicotinoyl-hydrazine (Anderson and associates[11]), since this substance inhibits the action of catalase equally to isoniazid (Bönicke[12]). The mechanism of the isoniazid resistance of tubercle bacilli also remains inexplicable by these hypotheses.

All of these facts, including the hitherto confusing finding of an "anti-isoniazid substance" in isoniazid-susceptible tubercle bacilli (Youmans and Youmans[13]), are coordinated by the following new hypothesis (figure 1) which is to be published in detail elsewhere.[14] According to this hypothesis, the action of isoniazid consists of seven steps, all of which are necessary for the inhibition of multiplication of isoniazid-susceptible tubercle bacilli in the concentration range from 0.01 to 0.1 γ per ml.

I. Isoniazid permeates readily through the bacterial cell membrane, so that its concentration becomes equal outside and within the bacterial cell.

II. Within the tubercle bacilli isoniazid is oxidized by peroxidase (Tirunarayanan and Vischer[15], Hedgecock and Faucher[16])—and possibly to a lesser degree by catalase—to isonicotinic acid and the oxidation products of hydrazine which are without further interest for the action of isoniazid.

III. Isonicotinic acid does not freely permeate through the bacterial cell membrane (Barclay and associates[17]), presumably because it exists as negative charged ion at pH above 6 (Black[18]). Therefore, isonicotinic acid is accumulated in tubercle bacilli and may be extracted by slightly acidic water (Boone and associates[19]).

IV. Isonicotinic acid or its amidation product isonicotinamide disturbs the activity of coenzyme I or II(di- or triphosphopyridine nucleotide) in a not exactly known way. Presumably an isonicotinamide analogon of coenzyme I (or II) is formed (*cf.* Zatman and associates[20]).

V. The disturbance of coenzyme I (or II) function is followed by the failure of the tubercle bacilli to oxidize substrate hydrogen by the cytochrome system forming water.

VI. By blocking the dehydrogenase-cytochrome system, a compensatory enhanced oxidation of substrate hydrogen by the autoxidable flavin enzymes is provoked, whereby the tubercle bacilli produce more hydrogen peroxide than usual.

VII. The enhanced production of hydrogen peroxide is the real cause of inhibition of cell multiplication presumably by the enhancement of catabolic processes.

The known antagonists of the antituberculous activity of isoniazid may be classified in the following manner:

1. Competitor at coenzyme I (or II) system and at peroxidase: nicotinoyl-hydrazine.

2. Competitors only at peroxidase: benzoyl-hydrazine and other carbonic acid hydrazides.

3. Hydrazone formers outside and within the tubercle bacilli: acetone, pyridoxal, sodium pyruvate, α-ketoglutarate.

[11] Anderson, K. F., *et al.*: Atti VI Congr. Intern. Microbiol. Roma, 1953, *1*, 517.
[12] Bönicke, R.: Ztschr. f. Hyg. u. Infektionskr., 1956, *142*, 347.
[13] Youmans, A. S., and Youmans, G. P.: Am. Rev. Tuberc., 1955, *72*, 196.
[14] Krüger-Thiemer, E.: Jber. Borstel, 1957, *4*, 299–509.
[15] Tirunarayanan, M. O., and Vischer, W. A.: Am. Rev. Tuberc., 1957, *75*, 62.
[16] Hedgecock, L. W., and Faucher, I. O.: Am. Rev. Tuberc., 1957, *75*, 670.
[17] Barclay, W. R., *et al.*: Am. Rev. Tuberc., 1954, *70*, 784.
[18] Black, M. L.: J. Phys. Chem., 1955, *59*, 670.
[19] Boone, I. U., *et al.*: Am. Rev. Tuberc., 1957, *76*, 568.
[20] Zatman, L. J., *et al.*: J. Biol. Chem., 1954, *209*, 453.

4. Isoniazid-oxidizing agents outside the bacterial cell: oxygen or hydrogen peroxide with heavy metal ions, hemin chloride, or peroxidase, potassium ferricyanide.

5. Hydrogen peroxide destroyers outside and within the bacterial cell: catalase, peroxidase, hemin chloride, cobalt-phthalocyanin, sodium pyruvate, α-ketoglutarate.

Living cells without peroxidase, e.g. isoniazid-resistant tubercle bacilli,[15] saprophytic mycobacteria,[15] many other bacteria and fungi,[15] and most animal cells,[21] are resistant to isoniazid in its therapeutic concentration range because they cannot accumulate isonicotinic acid and its metabolites.

Addendum

Nicotinamide is not an intermediate in the synthesis by erythrocytes of coenzyme I.[22] Since mycobacteria have an effective nicotinamidase,[23, 24] which is not inhibited by nicotinic acid, it may be that isonicotinamide is not an intermediate in the synthesis by mycobacteria of the insonicotinamide analogon of coenzyme I.

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June 13, 1957

[21] NEILANDS, J. B., *et al.*: Outlines of Enzyme Chemistry, John Wiley and Sons, Inc. New York, 1955, p. 220.

[22] PREISS, J., AND HANDLER, PH.: J. Am. Chem. Soc., 1957, *79*, 4246.

[23] GROSSOWICZ, N., AND HALPERN, Y. S.: Biochim. bioph. Acta, 1956, *20*, 576

[24] HALPERN, Y. S., AND GROSSOWICZ, N.: Biochem. J., 1957, *65*, 716.

Correspondence

PATHOGENESIS AND TREATMENT OF PULMONARY TENSION CAVITIES

To the Editor of the American Review of Tuberculosis and Pulmonary Diseases:

I would like to call attention to an oversight in the otherwise excellent article entitled "Pathogenesis and Treatment of Pulmonary Tension Cavities" by Benjamin P. Sandler which appeared in the September, 1957, issue of the REVIEW.

In his introduction, the author cites Eloesser (*J. Thoracic Surg.*, 1937, *7*, 1) as the first to use the term "blocked cavity." Actually, I believe the first use of this term should be attributed to Salkin, Cadden, and McIndoe, who published an article in the REVIEW in 1936 (*34*, 634) entitled "The Blocked Pulmonary Cavity. An Anatomical, Roentgenological and Clinical Study."

The source of Dr. Sandler's oversight was possibly the article of Vineberg and Kunstler published in 1944 which also credits Eloesser with the first use of the term. Another source of confusion might have been a misprint in Dr. Eloesser's bibliography which gives an incorrect page reference for the Salkin, Cadden, and McIndoe article.

VETERANS ADMINISTRATION HOSPITAL
SAN FERNANDO, CALIFORNIA

JOHN D. STEELE

November 1, 1957

Books

ANNUAL REVIEW OF MEDICINE. Vol. 8. By David A. Rytand and William Creger. Pp. 530, Annual Reviews, Inc., Palo Alto, California, 1957. Price, $7.50.

This volume, like its predecessors in the series, is a valuable guide to recent clinical investigations in most of the sub-specialty disciplines within internal medicine. The series is aimed primarily at those with teaching or investigative responsibilities, and, as the prospectus indicates, those ". . . whose background knowledge of the subject is already well-established" will find in the various sections not only an effective bird's-eye view of clinical research, but an excellent entry to the recent literature pertaining to specific problems.

Especially noteworthy in the current volume is the comprehensive review of recent gastroenterological literature by Gray and his associates, including brief but excellent sections on gastric secretion and peptic ulcer.

Also deserving of special mention are Earle's review on medical kidney disease and Grossman's on nutrition, including an excellent consideration of the recent literature on obesity. In addition, Fishman and Merritt have contributed an elegant chapter on diseases of the nervous system, and Bunim and Black have carefully reviewed recent work on the connective tissue (collagen) diseases.

Unfortunately, the familiar annotated list of *Reviews* has been omitted in this volume of the series; it is to be hoped that it will reappear shortly, since it enhanced the value of previous volumes as aids in dealing with the enormous amount of medical literature published each year.

This book contains something of value for everyone in internal medicine. It cannot be perused without profit.

JEREMIAH A. BARONDESS
New York

CARDIAC DIAGNOSIS: A PHYSIOLOGIC APPROACH. By Robert F. Rushmer. Pp. 447, W. B. Saunders Company, Philadelphia, 1955. Price, $11.50.

With the recent advances in the physiology and technology of cardiovascular research and treatment, there is need for a comprehensive review of the subject. This book satisfies the need and provides even more for the student of cardiac disease. The approach to diagnosis through basic physiology and the similarities as well as the differences in functional effects between various types of heart disease are stressed.

The subject matter is divided into five sections. The first deals with the anatomic, physical, and functional aspects of cardiac contraction, and the systemic and pulmonary vascular beds. The second part concerns the regulation of the peripheral vascular system and the cardiac output, with emphasis on hormonal and neural control. The third is devoted to cardiac reserve and congestive heart failure. The fourth presents a review of old and new diagnostic techniques, including pressure, roentgenography, electrocardiography, heart sounds and murmurs, and others. The usefulness and limitation of each technique is discussed. The last part consists of a discussion of etiologic heart disease and the application of the principles previously described. There is no attempt to provide a complete review of heart disease as evidenced by the classification in broad categories: myocardial ischemia, myocarditis, valvular heart disease, congenital heart disease, and possible heart disease.

The text is clear and easily understood by the novice as well as by the sophisticated reader. It is embellished with many illustrations which contribute to its clarity. The legends are complete and self-explanatory, their purpose being to render the figures independent of the text. When appropriate, an excellent summary completes a chapter.

The author is to be commended for his avoidance of complicated tables and graphs. Tedious discussions of controversial subjects are also avoided. There is a good bibliography however which provides a source of additional information for the interested reader.

A more thorough discussion of the clinical aspects of heart disease would be appropriate. The clinician, accustomed to think of diagnosis in terms of history and physical findings first and the laboratory second, will find the orientation different here. There is no discussion of cardiac treatment, an adequate subject for separate consideration elsewhere.

There is a great deal of basic and advanced information in this book, and it is presented in an orderly and unbiased manner. The medical student should find it helpful in bridging the gap between the basic and clinical sciences. The more experienced student of cardiology should find it valuable as a source of reference and review. The researcher may be attracted to the emphasis on the deficiencies in basic knowledge to which some attention has been devoted.

ALBERT L. RUBIN
New York, New York

BOOKS RECEIVED

EXPLORATION DE LA FONCTION RESPIRATOIRE. By H. Bour and P. Dejours. Pp. 50, Masson et Cie, Paris, France, 1957. Price, 600 fr.

RÉÉDUCATION FONCTIONNELLE PAR LA GYMNASTIQUE DANS LA TUBERCULOSE PULMONAIRE. By Torsten Bruce, Caroline Reuterswärd, and Birgit Westin. Pp. 110, Masson et Cie, Paris, France, 1957. Price, 950 fr.

TUBERKULOSE-JAHRBUCH 1954/55. By Rolf Griesbach. Pp. 295, Springer-Verlag, Berlin, Germany, 1957.

TUBERCULOSIS: EVERY PHYSICIAN'S PROBLEM. By J. Arthur Myers. Pp. 290, Charles C. Thomas, Springfield, Illinois, 1957. Price, $7.50.

American Trudeau Society

Medical Section of the National Tuberculosis Association

Obituaries

Harold Roosth
1915–1957

Harold Roosth of Tyler, Texas, died of a cerebral hemorrhage on February 7, 1957, in a Tyler hospital.

Dr. Roosth was born in that city on September 22, 1915, the son of Sam and Celia (Wengrow) Roosth. He attended Tyler public schools and Tyler Junior College, received a bachelor of arts degree from the University of Texas, Austin, in 1936, and earned his medical degree at the University of Texas Medical Branch in Galveston in 1940. He interned at St. Vincent's Hospital in Erie, Pennsylvania, until entering military service in 1941, and took his residency at John Sealy Hospital in Galveston from 1946 to 1948. Since that time, Dr. Roosth had practiced internal medicine in Tyler with his brother, Dr. Wiley Roosth.

Dr. Roosth was a medical officer during World War II, beginning as a first lieutenant in August, 1941, and being discharged in 1946 as a lieutenant colonel. He was a participant in four campaigns in the European theater. He was on the attending and consulting staffs of Medical Center Hospital and Mother Frances Hospital in Tyler. He was a member of the Smith County Medical Society, Eleventh District Medical Society, Texas Medical Association, American Medical Association, American Trudeau Society, American Diabetes Association, Texas and national geriatrics societies, Texas Tuberculosis Association, and Texas Heart Association. He was a past president of the Tyler Optimist Club; a member of B'nai Brith, Tau Delta Phi, and Phi Delta Epsilon fraternities.

He is survived by his wife and three children, Thomas, Cynthia Ann, and Marleen, of Tyler; and six brothers.

W. H. O., Jr.

Ray Hoyt Biggs
1906–1957

Ray Hoyt Biggs died at the Mississippi State Sanatorium on July 12, 1957, following a lengthy illness, at the age of 50 years.

Dr. Biggs was born in Jackson, Mississippi, on October 7, 1906. He received his elementary and high school education in the city schools of Jackson. He was graduated from the University of Alabama in 1928 with a B. A. degree. He obtained his medical certificate from the University of Mississippi in 1931, his M.D. degree from Emory University in 1933, and he interned at Fitkin Memorial Hospital, Neptune, New Jersey. He was awarded a Master of Public Health degree by Johns Hopkins University in 1938.

While serving as Madison County Health Officer at Canton, Mississippi, he developed pulmonary tuberculosis and entered the Mississippi State Sanatorium for treatment in 1938. After his disease was arrested in 1939 he joined the staff of the Sanatorium. In 1944 he was appointed Assistant Superintendent and Medical Director.

Dr. Biggs' professional life was characterized by integrity and intelligence, and complete

devotion to the welfare of his patients. His opinions were highly valued by his professional colleagues. He was author of several scientific papers, published in both local and national journals. He was a member of the Central Medical Society, the Mississippi Medical Association, the American Medical Association, the American Trudeau Society, and the American College of Chest Physicians. He was a deacon of the Presbyterian Church. He is survived by his widow, his daughter, and his mother.

C. A. W.

Roy Kenneth Smith

1885–1957

Roy K. Smith died on July 31, 1957, in Pasadena, California at seventy-two years of age. He was born at Lincoln, Kansas, on April 28, 1885.

Dr. Smith received an A.B. degree from the College of Emporia in 1905; an A.M. degree from the University of Kansas in 1909; and an M.D. degree from the University of Kansas in 1911. He took his internship at Severance Hospital, Seoul, Korea, 1911–1912. He became a medical missionary in 1911, and practiced medicine in this capacity until 1950 under the auspices of the Presbyterian Church.

He was interested in hospital construction and administration, and for ten years was superintendent of the Presbyterian Hospital, Chairyung, Korea. During one of his interchange periods, he served as a resident physician in the Kansas State Sanatorium for Tuberculosis and returned to Korea in 1946 as a director of tuberculosis sanatoriums.

After returning finally to the United States in 1950, he was made Chief of the Tuberculosis Service, Veterans Administration Hospital, Excelsior Springs, Missouri. He was a Fellow of the American Medical Association, American College of Physicians, member of the American Trudeau Society, the American College of Chest Physicians, and the American Academy of Tuberculosis Physicians. He was also a Diplomate of the American Board of Internal Medicine, specializing in pulmonary diseases.

He wrote many articles both for American and Korean medical journals. His publications were also printed in Chinese. Many of his articles were on the subject of tuberculosis in the Orient.

His hobby was philately and he belonged to several philatelic societies. One of his most notable contributions to the field of medicine has been his four sons, three of whom became outstanding physicians in their respective specialties: Dr. Kenneth M. Smith, of Santa Ana, California; Dr. Robert B. Smith, Grand Rapids, Michigan; Dr. Rodger B. Smith, Mason City, Iowa; and Albert M. Smith. Besides his four sons, he leaves a widow, Mrs. Lura McLane Smith, who resides at Duarte, California.

W. J. B.

NOTICES

The following dates and locations of the next two annual meetings of the National Tuberculosis Association and the American Trudeau Society have been selected and approved:

1958—Philadelphia, Pennsylvania—May 19–24

1959—Chicago, Illinois—May 24–29

POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Council on Postgraduate Medical Education of the American College of Chest Physicians will sponsor the Eleventh Annual Postgraduate Course on Diseases of the Chest at the Warwick Hotel, Philadelphia, March 3–7, 1958. The tuition fee is $75, including round-table luncheons.

Further information may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

FIFTH CONGRESS OF THE INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

The Fifth Congress of the International Society of Internal Medicine will hold its meeting in Philadelphia, April 23–26, 1958. The scientific program will include both morning and afternoon sessions.

General inquiries regarding the Congress should be addressed to Mr. E. R. Loveland, Secretary-General, 4200 Pine Street, Philadelphia 4, Pennsylvania.

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WANTED: Assistant Medical Director, 114 bed tuberculosis hospital, salary $8500-$9500 per year plus complete maintenance including apartment, food, laundry and utilities. Apply Executive Director, State Tuberculosis Hospital Commission, New Capitol Annex, Frankfort, Kentucky.

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WANTED: Full time physician for new 440 bed tuberculosis division of large general hospital in the East. Associated with two medical schools for teaching purposes with opportunity for research. Complete surgical and pathological facilities. Please address inquiries to Box #151, American Review of Tuberculosis and Pulmonary Diseases, 280 Madison Avenue, New York 16, New York.

WANTED: Immediately—Staff physician for newly constructed seventy-seven bed tuberculosis hospital, operated by the Ohio Department of Health. Experience in pulmonary diseases desired but not essential. Ohio license or eligibility for same required. Beginning salary $10,320 with yearly increases. Liberal vacation, sick leave, and retirement benefits. Furnished two bedroom apartment available at nominal rent. Apply Harold H. Cashman, M.D., Director, Southeast Ohio Tuberculosis Hospital, Nelsonville, Ohio.

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1958 ANNUAL MEETING

PHILADELPHIA, PENNSYLVANIA, MAY 18–23

The 1958 Annual Meetings of the National Tuberculosis Association, the American Trudeau Society, and the National Conference of Tuberculosis Workers will be held at Convention Hall, Philadelphia, Pa., May 18 to 23.

The ATS committee meetings will be held Friday, Saturday, and Sunday, May 16, 17, and 18.

Registration will begin Saturday afternoon, May 17, and continue through Sunday evening at the Bellevue-Stratford Hotel. Beginning Monday, May 19, registration, the exhibits program, and regular daytime sessions will be held at Convention Hall. Evening sessions through the week will be held at the Bellevue-Stratford.

Medical, public health, and nursing sessions will begin on Monday, May 19. General sessions will include an opening keynote program Monday A.M., the awards session Wednesday evening, and a session Thursday morning, May 22.

Blocks of rooms have been reserved in the following hotels.

Bellevue-Stratford. Rates: single, $9–11; double, $15; twins, $12—17.
Adelphia. Rates: single, $7—10; double, $12—14; twins, $13—16.
John Bartram. Rates: single, $7; double, $9.50—10.50; twins, $10.50—12.50.
Sheraton. Rates: single, $9.85—12; twins, $14—17.
Sylvania. Rates: single, $7—7.50; twins, $11.50—13.50.
Warwick. Rates: single, $11; double, $13—16; twins, $14—19.

Special bus service will be provided between these hotels and Convention Hall.

Applications for rooms should be made directly to the hotel of choice. *Requests must include mention of NTA Annual Meeting and give a definite date and hour of arrival as well as a date of departure. Names and addresses of all persons who will occupy the rooms requested must be included.* In the event the hotel is unable to provide the desired space, requests will be referred to the Philadelphia Convention Bureau for clearing with another one of the cooperating hotels. Confirmation will come direct from hotel accepting reservation.

The Behavior of Pulmonary Tuberculous Lesions

by E. M. MEDLAR, M.D.

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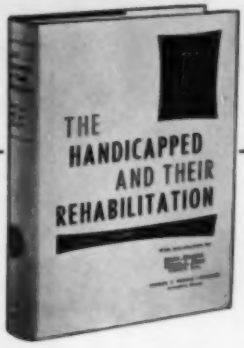

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Describes in fourteen chapters the many disabilities which offer opportunities for rehabilitation services. For example, in a special chapter on "Tuberculosis," Dr. Harry A. Pattison, the editor of this volume, answers these questions:

- **What is Tuberculosis?**
- **Who Has Tuberculosis?**
- **How Do People Contract Tuberculosis?**
- **How Is Its Presence Determined?**
- **What Can Be Done for the Tuberculous?**

Edited by
HARRY A. PATTISON, M.D., F.A.C.P.
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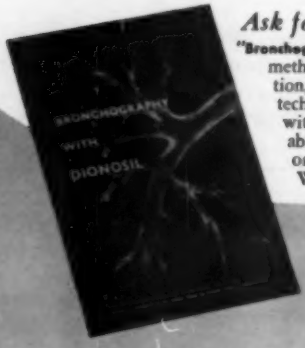

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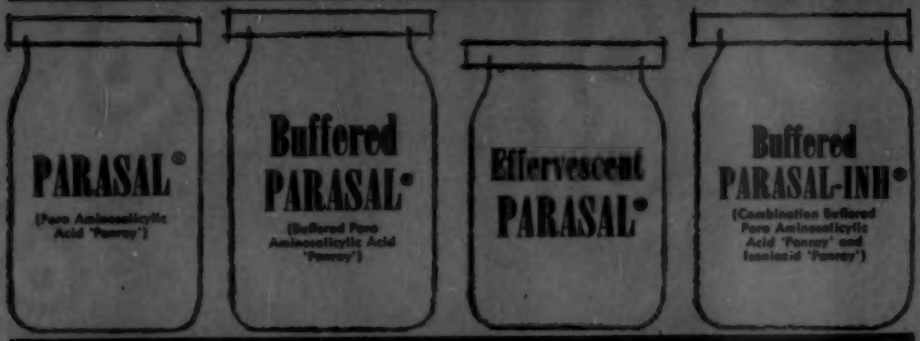

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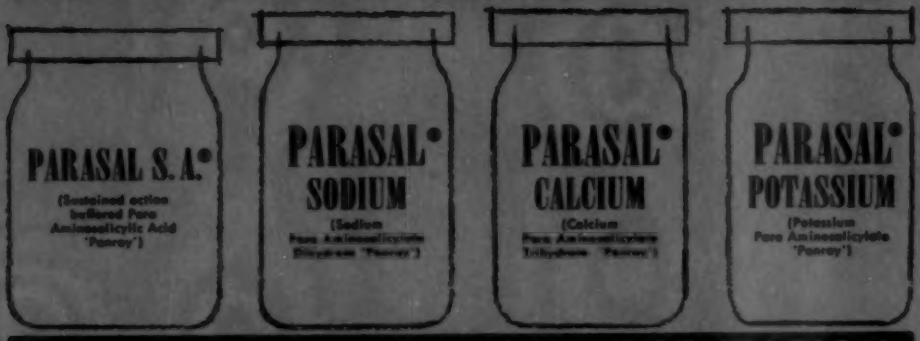
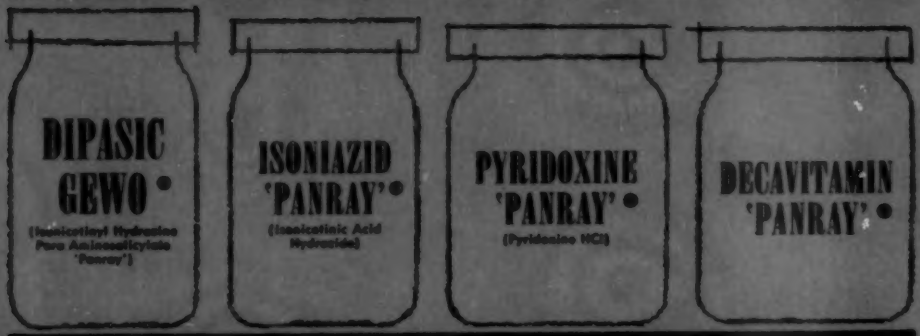


for QUALITY... ECONOMY... REPUTATION



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